Appendix A – Journal submission cover letter

Reference: Effect of exercise, cognitive, and dual-task interventions on cognition in type 2 diabetes mellitus: A systematic review and meta-analysis.

30th September 2019

Dear editor,

We wish to submit the above systematic review and meta-analysis for consideration by PLOS ONE. We can confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

We have selected PLOS ONE as this systematic review and meta-analysis is interdisciplinary and will be of interest to the wide ranging readership of PLOS ONE, including those working in diabetes management, health psychology research, and policy and guideline making. With this rapidly evolving area of research we also wish our findings to be available to all and without restriction so as to inform both future research and the management of cognitive dysfunction in individuals with type 2 diabetes.

Individuals with type 2 diabetes have an increased risk of developing severe cognitive dysfunction. Non-pharmacological interventions including exercise, cognitive and dual-task training have been shown to be effective in improving cognition in healthy cohorts. Whilst no previous review has evaluated the effects of cognitive or dual-task training in type 2 diabetes, previous narrative reviews on the effects of exercise report inconsistent findings. This review aimed to systematically review the evidence, and estimate the effects, of exercise, cognitive, and dual task interventions on cognition in type 2 diabetes.

This systematic review was based on a clearly formulated question using systematic and explicit methods to identify, evaluate and synthesise relevant primary research. This systematic review was reported following the Preferred Reporting Items for Systematic review and Meta-Analysis' (PRISMA) guidelines. The key findings were:

1. We provide the first statistical evidence of synthesised data from interventional trials assessing the effects of exercise on cognition in type 2 diabetes.
2. We provide the first evaluation of the effects of cognitive and dual-task trials on cognition in type 2 diabetes.
3. There are few high quality randomised controlled trials in the area.

On behalf of myself and co-authors, I sincerely thank you for taking time to consider our submission.

Yours sincerely,

Samuel Cooke

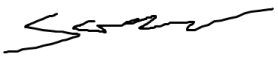
Appendix B – Response to reviewers

10th March 2020

Dear editors and reviewers,

We thank you sincerely for your review of our manuscript, it was very useful and by addressing your comments we think you have helped us to significantly improve our manuscript. Please find the Author's response to all comments below.

On behalf of all authors I thank you sincerely,



Samuel Cooke

Reviewer #	Comment	Author response/amendments
Journal requirement	Please ensure that your manuscript meets PLOS ONE's style requirements, including those for file naming.	Headings changed to appropriate levels and file named appropriately.
Journal requirement	Please make sure that all items in the PRISMA checklist have been performed in your manuscript. For instance, please provide i) the full electronic search strategy for at least one database, including any limits used, such that it could be repeated; ii) In the main text and in the PRISMA diagram, please report the detailed reasons for excluding articles at each stage of your systematic review. Thank you for your attention to these requests.	Full electronic search strategy for PubMed added as a supplementary material file - **S2 Electronic search strategy**. In text search terms amended and sentence added referring to supplementary material **(Lines 125 – 129).** Detailed reasons for exclusion of trials included in text **(Lines 182 - 185**) and in the PRISMA diagram (fig 1.)
Reviewer #1	The authors should provide more detail on how exercise would affect cognitive functioning among individuals with Type 2 diabetes (directly or indirectly--improving glycemic control).	Mechanisms of exercise training are discussed in the introduction and additional information has been added to the discussion **(Lines 344 - 352).**
Reviewer #2	I would recommend an update of the searches from March 2019 to now. This will ensure that any new trials have not been missed, and the review is up to date. Currently, the searches are nearly a year out of date.	Searches have been updated to March 2020. **(Line 123)** One additional exercise trial was identified that met the review eligibility criteria and was included in the review but could not be included in meta-analyses. The in-text references and reference list have been updated throughout.
Reviewer #2	The authors have used the change from baseline score in the meta-analysis (to include more trials). Would the authors like to comment on whether using post intervention values (from the trials that presented this data) changed the pattern of results for the meta-analyses? I wonder whether this may be added narratively to the results section.	Passage added showing the meta-analysis of trials using post intervention values **(Lines 277 - 281).**
Reviewer #2	Line 64 – Remove "cardiovascular disease" as it is an umbrella term for many of the conditions listed e.g. "myocardial infarcts" and "stroke".	'Cardiovascular disease' has been removed from **(Line 62).**
Reviewer #2	Line 125 – Capital S for "Scholar"'.	Capital S added **(Line 123)**
Reviewer #2	Line 139 – Should be lower case "d" for "diabetes".	Lower case d added **(Line 141)**
Reviewer #2	Line 308-309 –Would the authors care to comment on the inconsistent findings between the previous reviews? Was the inclusion/exclusion criteria different between these reviews?	Sentence "The findings of these reviews are inconsistent." removed from **(Line 324)** and sentence added suggesting the differences are attributed to the inclusion of trials with different study designs etc **(Line 326 - 328).**
Reviewer #2	Line 318- I am unclear what the authors mean by the term "clinically meaningful". Do the authors have evidence that those observed effect sizes have clinical implications for cognitive function? I would recommend the removal of this term here and throughout the manuscript (including conclusion).	**Line 41** – abstract conclusion – term removed **Line 336** – amended **Line 441** – amended
Reviewer #2	Line 341-343- Needs rewriting.	This sentence has been rewritten **(Line 369 -371).**
Reviewer #2	Lines 394-396- There is a lack of references regarding interventions that have been shown to be important for the type 2 diabetes population?	Added 3 references to support this statement **(Line 421 - 422).**
Reviewer #2	Some repetition in the discussion. E.g. Lines 341-343 and Lines 390-392. Lines 367-368 and 387-388.	Lines 390 – 392 – Initial sentence removed (**Lines 417-419**) and replaced with amended sentence **(Lines 418 - 419).** Lines 387-388 amended **(Lines 413 - 415).**

Appendix C - PROSPERO study protocol

Investigating the effect of exercise, cognitive, and dual-task interventions upon cognitive function in type 2 diabetes mellitus

Samuel Cooke, Hayley Robinson, Laura Simmons Arwel Jones, Chris Bridle, Ffion Curtis

Citation

Samuel Cooke, Ffion Curtis, Chris Bridle, Arwel Jones, Hayley Robinson, Laura Simmons. Investigating the effect of exercise, cognitive, and dual-task interventions upon cognitive function in type 2 diabetes mellitus. PROSPERO 2017 CRD42017058526 Available from :https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017058526

Review question

What are the effects of exercise interventions upon cognitive function in type 2 diabetes?

What are the effects of cognitive interventions upon cognitive function in type 2 diabetes?

What are the effects of dual-task interventions upon cognitive function in type 2 diabetes?

Searches

The following electronic databases will be searched for completed and ongoing trials: PubMed, EMBASE, CINAHL, PsycINFO, Web of Science, ClinicalTrial.gov, and the Cochrane Central Register of Controlled Trials (CENTRAL). Conference papers indexes will, in addition, be searched to obtain non-published data, and we will also include a search of the Cochrane databases and PROSPERO for any ongoing or completed systematic reviews, and the databases of the National Health Service Centre for Reviews and Dissemination: Health Technology Assessment (HTA) and Database of Abstracts of Reviews of Effects (DARE). All databases will be searched from their inception, and no limits on language will be set. Reference lists of all potentially relevant studies identified by the database searches will be screened, and both primary and secondary searches will be supplemented with internet searches

(Google Scholar). If required, contact with study authors, experts and research groups will be made to retrieve data/information from included trials and reviews.

Types of study to be included

Studies will be considered for inclusion if they are randomised controlled trials that have allocated participants at an individual or cluster level, or via a quasi-randomised method. Review articles will also be retrieved to supplement searching.

Condition or domain being studied

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, characterised by hyperglycaemia, and precipitated as a result of abnormalities in glucose metabolism (Scheen, 2003). Evidence suggests that T2DM is associated with an accelerated or increased risk of cognitive decline, increasing the risk of dementia (Reijmer et al, 2010). Exercise, cognitive, and dual-task interventions have been shown effective in improving cognition in healthy populations (Theil et al., 2013; Eggenberger et al., 2015), although the effects of such interventions upon cognition in T2DM are unclear.

Participants/population

The population of interest in this review are adults (aged 18+) who have been diagnosed with T2DM.

Intervention(s), exposure(s)

Studies will be considered for inclusion if they have investigated the effects of either an exercise, cognitive or dual-task intervention on any domain of cognitive function in individuals diagnosed with T2DM. In the case that an insufficient number of studies are retrieved for the T2DM population, type 1 diabetes mellitus will also be considered for inclusion. Eligible exercise interventions will include any structured/organised exercise training intervention. Eligible cognitive interventions will include any task-based cognitive training or computer-based cognitive training. Eligible dual-task interventions will

include simultaneous exercise-cognitive training, e.g. treadmill walking whilst simultaneously performing a memory recall task.

Comparator(s)/control

Control group/usual/standard care.

Main outcome(s)

Cognitive function. This will include any measure of the effects of a given intervention upon any domain(s) of cognitive function using a validated measurement tool.

Additional outcome(s)

None.

Data extraction (selection and coding)

Data extraction will take place using an adapted Cochrane data extraction template for interventions. One reviewer will undertake data extraction for each study, which will be cross-checked by a second reviewer. Papers will be compiled using EndNote referencing software. The following study characteristics will be extracted: **Methods**: title, date, author, study aim, study design, recruitment methods, inclusion/exclusion criteria, study and intervention duration, outcome, and unit of allocation. **Population characteristics**: age, gender, length of diagnosis, co-morbidities, and other relevant demographics. **Intervention/comparator**: intervention groups, sample size of each group, intervention description (site of delivery, modality, duration, intensity, frequency, and follow-up), and delivery of intervention e.g. trained professionals, supervised/unsupervised. **Outcome measurements**: primary and secondary outcome names, outcome definition, unit of analysis, individual reporting/measuring outcomes, missing data, withdrawals, exclusions, and participants lost to follow-up.

Risk of bias (quality) assessment

Two reviewers will independently assess risk of bias for each included study using the Cochrane risk of bias table. The following domains will be evaluated: selection bias (random sequence generation and allocation concealment); detection bias (blinding of outcome assessment); attrition (incomplete outcome data); reporting bias (selective outcome reporting); and other bias. Each domain will be classified as having either a high, low, or unclear risk of bias. The following criteria will be used to categorise each domain as having an adequate, unclear, or inadequate risk of bias for each study:

(i) Low risk of bias (all criteria are graded as adequate);
(ii) Moderate risk of bias (one criterion graded as inadequate, or more than two graded unclear);
(iii) High risk of bias (more than one criterion graded as inadequate, or more than two graded unclear).

Discrepancies between reviewers' judgments regarding the risk of bias for certain studies will be settled through further discussion with a third reviewer. Considering the type of interventions to be included, the domain performance bias (the blinding of participants and personnel to treatment allocation) will not be expected to be of relevance, and therefore will not be assessed.

Strategy for data synthesis

Extracted data will be independently analysed by one reviewer using RevMan and then cross-examined by a second reviewer for accuracy purposes. Studies will be pooled together based upon the intervention type (e.g. exercise, cognitive, or dual-task) and a sub-analysis performed to quantify the effect of each type of intervention upon cognition in T2DM. Data will be quantified using a random-effects meta-analysis, with standardised mean differences and 95% confidence intervals calculated for continuous outcomes and risk ratios given for binary outcomes. An I-squared threshold of >40% will be set for the detection of heterogeneity. In the event that studies exhibit heterogeneity, a sensitivity analysis will be performed, but in case meta-analysis is not possible, we will conduct a narrative synthesis of the findings from the included studies.

Analysis of subgroups or subsets

Depending on the studies included, sub-analyses may be conducted based upon the frequency, duration, intensity, or modality of interventions, the outcome measurements, the cognitive status, or the length of disease diagnosis.

Contact details for further information

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Organisational affiliation of the review

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http://lih.lincoln.ac.uk/

Review team members and their organisational affiliations

Mr Samuel Cooke. Lincoln Institute for Health, University of Lincoln

Dr Ffion Curtis. Lincoln Institute for Health, University of Lincoln

Professor Chris Bridle. Lincoln Institute for Health, University of Lincoln

Dr Arwel Jones. Lincoln Institute for Health, University of Lincoln

Miss Hayley Robinson. Lincoln Institute for Health, University of Lincoln

Miss Laura Simmons. Lincoln Institute for Health, University of Lincoln

Type and method of review

Systematic review

Anticipated or actual start date

01 February 2017

Anticipated completion date

01 September 2017

Funding sources/sponsors

None

Conflicts of interest

None known

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Cognition; Cognitive Dysfunction; Diabetes Mellitus, Type 2; Exercise; Exercise Therapy; Humans; Neurobehavioral Manifestations; Risk Factors; Task Performance and Analysis; Treatment Outcome

Date of registration in PROSPERO

03 March 2017

Appendix D – PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7,8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7,8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7,8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12,13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13,14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12,13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13,14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15,19,20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17,18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Appendix E – Example electronic database search

PubMed: full electronic search strategy (from inception to March 2020)

1. mh. Type 2 diabetes mellitus
2. Type 2 diabetes
3. Type II diabetes
4. mh. Adult-onset diabetes mellitus
5. Adult-onset diabetes
6. mh. Non-insulin dependent diabetes mellitus
7. Non-insulin dependent diabetes
8. mh. Maturity onset diabetes mellitus
9. Maturity onset diabetes
10. Late onset diabetes
11. mh. Slow onset diabetes mellitus
12. Slow onset diabetes
13. Diabetic
14. T2DM
15. t2d
16. mh. NIDDM
17. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. mh. Exercise
19. Exercise
20. Exercise training
21. Exercise intervention
22. mh. Aerobic exercise

23. Aerobic exercise
24. Aerobic training
25. mh. Physical activity
26. Physical activity
27. mh. Physical exercise
28. Physical exercise
29. Physical training
30. Exergaming
31. Cognitive training
32. Cognitive intervention
33. Cognitive remediation
34. Brain training
35. Computerized training
36. Memory training
37. Attention training
38. Dual task
39. Dual task training
40. Dual task intervention
41. Dual-task
42. Dual-task training
43. Dual-task intervention
44. Motor-cognitive
45. Multi-task
46. Divided attention

47. 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46
48. mh. Cognition
49. Cognit*
50. Neurocognitive function
51. Brian funct*
52. Mild cognitive impairment
53. Mini-mental state examination
54. Global cognitive function
55. mh. Executive function
56. Executive function
57. Memory
58. mh. Attention
59. Attention
60. 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59
61. 17 AND 47 AND 60

Appendix F – Ethical approval application

SCHOOL OF PSYCHOLOGY ETHICAL APPROVAL FORM FOR HUMAN PARTICIPANTS

Tick relevant boxes: ☐ **STAFF Project** × **POSTGRADUATE Project** ☐ **TRACK A**
☐ **UNDERGRADUATE Project** × **TRACK B**
☐ **ROUTINE EXTENSION TO STUDY**

Title Of Project: Walking, cognitive, and dual-task interventions in type 2 diabetes mellitus: A methodological development study.
Name of researcher(s): Samuel Cooke
Name of supervisor: Dr. Ffion Curtis, Dr. Kyla Pennington, Dr. Mark F Smith **Date:**6/29/17

		YES	NO	N/A
1	Will you describe the main procedures to participants in advance, so that they are informed in advance about what to expect?	**X**		
2	Will you tell participants that their participation is voluntary?	**X**		
3	Will you obtain written consent for participation?	**X**		
4	If the research is observational, will you ask participants for their consent to being observed / taped?	**X**		
5	Will you tell participants that they may withdraw themselves or their data from the research at any time, that no reason needs to be given, and that they can do so without losing any rewards (if applicable)?	**X**		
6	Will you give participants the option of declining to give information they do not want to give (e.g., not filling out all questions in a questionnaire)?	**X**		
7	Will you tell participants that their data will be treated with full confidentiality, and stored securely (for 7 years at the minimum) and that, if published, it will not be identifiable as theirs?	**X**		
8	Will you debrief participants at the end of their participation (i.e. give them a brief explanation of the study)?	**X**		

If you have ticked **No** to any of Q1-8, but have **ticked box A** overleaf, please give any explanation on a separate sheet. (Note: N/A = not applicable)

		YES	NO	N/A
9	Will your project involve deliberately misleading participants in any way?		**X**	
10	Is there a realistic risk of any participants experiencing either physical or psychological distress or discomfort? If **Yes,** give details on a separate sheet and state what you will tell them to do if they should experience any problems (e.g. who they can contact for help).	**x**		

If you have ticked **Yes** to 9 or 10 you should normally **tick box B** overleaf; if not, please give a full explanation on a separate sheet.

			YES	NO	N/A
11	Do participants fall into any of the following special groups? If they do, please refer to the appropriate BPS guidelines, and **tick box B** overleaf. **Please note that you may also need to gain satisfactory CRB clearance or equivalent for overseas participants.**	School children (under 18 years of age)		**X**	
		People with learning or communication difficulties		**X**	
		Patients		**X**	
		Those at risk of psychological distress or otherwise vulnerable		**x**	
		People in custody		**X**	
		People engaged in illegal activities (e.g. drug taking)		**X**	

There is an obligation on the lead researcher to bring to the attention of the School's Ethics Committee projects with ethical implications not clearly covered by the above checklist.

PLEASE TICK **EITHER** BOX A or BOX B BELOW AND **PROVIDE THE DETAILS REQUIRED** IN SUPPORT OF YOUR APPLICATION, THEN SIGN THE FORM.

Please tick:

A. I consider that this project has **no** significant ethical implications to be brought before the Departmental Ethics Committee.	

In less than 150 words, provide details of the study including the rational, the number and type of participants, methods and tests to be used (i.e. the procedure).

This form (and any attachments) should be submitted to the school's Ethics Committee where it will be considered by the Chair before it can be approved.

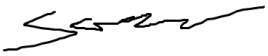
B. I consider that this project **may** have ethical implications that should be brought before the Departmental Ethics Committee, and /or it will be carried out with children or other vulnerable populations.	**X**

Please provide details of the project on an EA2 University Ethics for Human Participant taking into account the following advice:

1. Be clear about the purpose of the project and its academic rationale.
2. Briefly describe the methods / measurements and parties involved / affected.
3. Be clear about recruitment methods, numbers used, age, gender, exclusion/inclusion criteri handling procedures for field experiments, etc.
4. Include concise statements of the ethical considerations raised by the project (including care and aftercare) and how you intend to deal with them.
5. Include all relevant materials, such as consent form, participant information form, debrief, questionnaire / stimulus materials, letters /posters to recruit, etc**.**

This form should be submitted to the School's Ethics Committee for consideration.
If any of the above information is missing, your application will be returned to you.

I am familiar with the BPS Guidelines for ethical practices in psychological research, and the University Regulations for Ethical Research (and have discussed them with other researchers involved in the project or my supervisor.

Signed:  Print Name: Samuel Cooke Date: 05/07/2017
(PG Researcher(s), if applicable) Email: **scooke@lincoln.ac.uk**

Signed:  Print Name: Ffion Curtis Date: 05/07/2017
(Lead Researcher or Supervisor) Email: **Fcurtis@lincoln.ac.uk**

STATEMENT OF ETHICAL APPROVAL

This project has been considered using agreed Departmental procedures and is now approved.

Signed…….Print Name……..Date……..

(Chair, Departmental Ethics Committee)

EA2

Ethical Approval Form: Human Research

Please word-process this form, handwritten applications will not be accepted

This form must be completed for each piece of research activity whether conducted by academic staff, research staff, graduate students or undergraduates. The completed form must be approved by the designated authority within the Faculty.mailto:jgreen@lincoln.ac.uk

Please complete all sections. If a section is not applicable, write N/A.

1 Name of Applicant	Samuel Cooke	
	Department: Lincoln Institute for Health	**Faculty:** School of Health and Social Care
2 Position in the University	PhD Student	
3 Role in relation to this research	Principal Investigator	
4 Brief statement of main Research Question	What is the most optimal methodological approach to investigating exercise, cognitive, and dual-task intervention for improving cognitive function in type 2 diabetes mellitus?	
5 Brief Description of Project	**Background/Aim** Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by hyperglycaemia and precipitated as a result of abnormalities in glucose metabolism[1, 2]. The disorder is strongly associated with both microvascular and macrovascular complications including retinopathy, nephropathy, neuropathy, cardiovascular disease and cerebrovascular disease, increasing the risk of tissue and end organ damage[3, 4]. In addition to these "classic" diabetic complications, there is evidence to suggest that T2DM may also has a deleterious impact upon cognitive function[5-7]. Ageing is associated with a progressive deterioration in the structure of the human brain leading to a decline in cognitive function[8, 9], with evidence pointing towards an accelerated decline associated with T2DM[10, 11]. Ultimately, evidence has shown that individuals with T2DM have an increased risk of developing severe brain complications, including cognitive dysfunction, dementia, and Alzheimer's disease compared to their healthy counterparts[12, 13]. Regarding strategies to ameliorate cognitive function, both exercise and cognitive interventions have been shown to be effective in reducing the rate of cognitive decline within both healthy and diabetic populations[14-16]. Emerging evidence from studies within healthy cohorts suggest that dual task interventions encompassing simultaneous physical and cognitive activities (e.g. treadmill walking whist performing a cognitive task) may be superior in improving cognitive function compared to single task interventions[17-19]. Yet, it remains unknown as to what effect a dual task intervention may have upon cognitive function within a T2DM population. In order to conduct this investigation, an appropriate methodology needs to be developed informed by previous evidence. Therefore, the aim of this methods development study is to	

conduct a series of walking, cognitive, and dual task sessions that will be used to inform the development of methods for interventions aiming to improving cognitive function in T2DM. In addition, this study will also pilot the cognitive outcome assessment measures.

Study design

The purpose of this study is to develop the methodology of the main experimental studies of this PhD project. This study will utilise a cross-over research design whereby individuals will be required to participate in a four-week programme involving walking, cognitive, and dual task activities informed by evidence identified in study 1 "*Investigating the effects of exercise, cognitive, and dual-task intervention upon cognitive function with type 2 diabetes mellitus: A systematic review and Meta-Analysis*". Participants will then be invited to discuss their experience of each intervention, including the outcome measure procedures (neuropsychological test battery), as part of a focus group at the end of the programme alongside an evaluation questionnaire.

Participants

This study will aim to recruit approximately ten individuals with T2DM. Individuals will be included in this study if they meet the following inclusion criteria:

- Diagnosed with T2DM
- Aged 25-69 years
- Are currently working, studying or is a relative/friend of an individual working or studying at the University of Lincoln.

Individuals will be excluded from this study if they meet the following exclusion criteria:

- Diagnosed with type 1 diabetes mellitus, or any other significant medical condition/complication e.g. heart disease, cancer, respiratory disorders etc. or physical limitation identified using the physical activity readiness-questionnaire (PAR-Q) form
- Are diagnosed with cognitive impairment as identified using the mini-mental state examination (MMSE)
- Are not aged 25-69
- Do not work/study or know anybody working/studying at the University of Lincoln.

Recruitment strategy

Ten individuals diagnosed with T2DM will be recruited internally from within the University of Lincoln's student and staff population. The main recruitment strategies include:

- Contacting and liaising with the University of Lincoln Diabetes Support Group
- The dissemination of posters and flyers around the university campus
- Invitation emails sent to both staff and student mailing lists
- Poster invitations posted on the staff and student news feeds.
- External recruitment through word of mouth e.g. friends and family

Study protocol

Participants will be required to attend a four-week programme located at the University of Lincoln. The programme will require participants to complete an initial preliminary study visit followed by two sessions a week comprising of walking, cognitive, and dual-task activities. Week 1 will consist of two 40-minute treadmill walking sessions, week 2 will consist of two 40 minute cognitive sessions (e.g. performing memory recall, verbal fluency, auditory memory tasks etc), and week 3 will consist of two 40-minute dual-task sessions (treadmill walking whilst simultaneously performing a cognitive task). Week 4, participants will complete a series of computer based cognitive tests as part of a neuropsychological test battery[20] in addition to completing a study evaluation questionnaire. Finally, participants will then have the opportunity to take part in a focus group discussion to feedback on their experience of the study participation (acceptability of all elements of the interventions and outcome measurements: time, delivery, venue, difficulty etc.). All study visits will take place in the Department of Sport and Exercise Science, University of Lincoln, with exception of week 4 which will take place in the Department of Psychology.

Preliminary study visit

Prior to week 1, participants will be invited to take part in a pre-intervention familiarisation visit. The purpose of this visit is to obtain informed consent from participants and review and complete the physical activity readiness questionnaire (PAR-Q) and mini mental state examination (MMSE), see instrumentation and data collection section for more details. Participants will also be familiarised with the procedures and equipment used in each type of session e.g. treadmill walking, cognitive tasks, using the Borg Rating of Perceived Exertion scale etc. In addition, advice will be given on the appropriate attire to wear during the walking visits along with addressing any questions that participants require answering.

Week 1 – walking phase (Session 1 & 2)

Session1

Initially participants will be required to re-read the participant information sheet or confirm that they are clear and understand the study protocol. This is also an opportunity for participants to ask any questions with regards to the study. Treadmill walking will begin with participants completing a 5-minute warm up performed at a self-selected intensity. Following this, participants will then treadmill walk at a perceived exertion of 11-13 as measured by the Borg scale of perceived exertion[21], which has been shown to correspond to a low intensity of exercise[22], for a duration of 40 minutes[20, 23]. Once completed, the session will then be followed by a 5-minute cool down period performed at a self-selected intensity. For the purpose of potentially measuring walking intensity using a heart rate (HR) method (e.g. HRreserve or HRmax) in the main experimental studies, HR will be recorded throughout using wireless HR monitors.

Session 2

Session 2 will follow the same procedure as session 1.

Week 2 – cognitive task phase (Session 3 & 4)

Session 3

The first cognitive session will require the participant to perform a series of different cognitive tasks. Each cognitive task will be conducted for approximately 5-10 minutes with the session duration lasting approximately 40 minutes. The difficulty will remain low for the duration of this session. The following cognitive exercises will be practiced 1) verbal fluency[24] 2) Visual attention[24] 3) Auditory memory[24] 4) Memory recall[25] 5) Mental arithmetic

task[26] and 6) the stroop task[27]. Details of each task can be found under instrumentation and data collection.

Session 4

Session 4 will follow the same protocol as session 3, with the exception that the difficulty of some cognitive tasks will increase throughout the session. Details of varying difficulties of each task can be found under instrumentation and data collection.

Week 3 – dual task phase (Session 5 & 6)

Session 5

Week 5, participants will be required to complete the dual-task phase. Session 5 will combine methods from both the walking and cognitive phase in that participants will walk on the treadmill whilst performing cognitive tasks. This session will follow the same structure as session 1 e.g. 5 minute warm up, 40 minutes walking-cognitive tasks, 5 minute cool down The difficulty of each cognitive task will remain low in this session.

Session 6

Session 6 will follow a similar protocol to session 5 with the exception that the difficulty of certain cognitive tasks will increase throughout the session.

Week 4 (Session 7 & 8)

During the final phase of this study, participants will be invited to complete a computerised neuropsychological test battery in addition to completing an evaluation questionnaire during the first session. During the final session of the study participants will be invited to join a focus group discussion in which the session will be recorded and transcribed. The final phase of this project will be conducted in psychology labs, Sara Swift building.

Session 7

Participants will be required to conduct a computerised neurological test battery that will assess their cognitive function. The test battery is performed on a specialist touch screen laptop using software provided by Cambridge Cognition - Cambridge Neuropsychological Test Automated Battery (CANTAB), the international gold standard for digital cognitive research. T2DM is a risk factor for dementia and Alzheimer's disease therefore participants will be tested using a prodromal Alzheimer's/mild cognitive impairment test battery. This test battery has been shown to be highly sensitive to cognitive dysfunction showing clinically meaningful outcomes associated with impaired day to day function. This test battery will take approximately 35 – 45 minutes to complete. The test battery includes tests such as:

- Motor screening task
- Reaction time
- Paired associated learning
- Spatial working memory
- Pattern recognition memory
- Delayed matching to sample
- Rapid visual information processing

In addition, each participant will also be required to complete an evaluation questionnaire regarding their thoughts and experiences of the study at the end of this session. Details of each cognitive task can be found under instrumentation and data collection.

Session 8

The final session of this research project participants will be invited to attend a focus group with the aim of discussing each individual's thoughts and experiences of each element of the 3 intervention arms as well as the computerised neuropsychological test battery. The discussion will be guided using prompts and open-ended questions and recorded and transcribed. The group discussion will last approximately 1-2 hours in duration. Once participants have completed this session, the project will be complete.

Data collection, storage and instrumentation

Data collection

Data will be collected during the preliminary visit (Informed consent, MMSE, PAR-Q), during session 1 & 2 (HR), session 3 & 4 (cognitive task scores), session 5 & 6 (cognitive task scores, HR, evaluation questionnaire) and session 7 & 8 (computerised test battery scores & focus group recordings). The administration and collection of tools and data collection will be conducted by the principal investigator.

Data storage

Personal data, research data and the linking code will be stored in separate locations. When stored electronically, this will include using encrypted digital files within password protected folders and storage media. Personal information shall be stored separately to research data and will be kept secure, and maintained. Physical storage may include (but not limited to) locked filing cabinets with restricted access/locked office. In accordance with the University of Lincoln's policy, data will be kept intact for five years at least and will be deleted or destroyed in accordance with all legal, ethical, research funder and organisational requirements and with particular concern for confidentiality and security.

Guidance regarding withdrawal

Participants shall be withdrawn from study if consent is withdrawn – it shall be noted that data should not/cannot be destroyed, as it should be possible to recreate a participant's participation up to the point of withdrawal. Participants should also be made aware that withdrawal will not affect their future care/employment/involvement in future studies. Participant should also be made aware that data may still be used in the final analysis where data analysis has already taken place.

Instrumentation

Physical activity readiness questionnaire (PAR-Q)

The PAR-Q form is a preparticipation health screening tool used to evaluate individuals with medical contraindications that require exclusion from exercise programs until those conditions have been abated or controlled. The form consists of seven questions that helps identify underlying medical conditions/risk factors that may prevent an individual from participating in exercise or require them to seek medical approval prior to participation. If participants answer yes to one questions or more they will be required to contact their doctor to clarify that it is safe for them to become physically active at this current time and in their current state of health. If they answer no to all questions, they will be eligible to participate in the study. If a participant does answer yes to one or more questions, they are required to state that they have sought medical advice and that their doctor has approved their participation.

Mini-mental state examination (MMSE)

The MMSE is the most commonly used test for complaints of problems with memory or other mental abilities. It can be used by clinicians/researchers to help diagnose/screen for dementia and to help assess its progression and severity. It consists of a series of questions and tests, each of which scores points if answered correctly. The MMSE tests a number of different mental abilities, including a person's memory, attention and language. An individual can score between 0 and 30 on the MMSE with the cut off score for mild cognitive impairment being <23. If any MMSE scores outside of the 0-23 range is identified participants will be reassured that cognitive decline is a natural process associated with ageing and that the tests scores are only indicative and provide no clinical diagnosis. If concerned, participants will be advised to seek further information from their GP.

The Borg scale

The Borg Rating of Perceived Exertion is a way of measuring physical activity intensity level. Perceived exertion is how hard an individual feels their body is working. It is based on the physical sensations a person experiences during physical activity, including increased heart rate, increased respiration or breathing rate, increased sweating, and muscle fatigue. The scale ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." The scale will be presented to the participant during treadmill walking in which they will be required to verbally identify a number on the scale which will reflect that individual's subjective perception of effort.

Prodromal MCI test battery

The prodromal Alzheimer's/MCI test battery identifies baseline impairment in Alzheimer's disease/MCI. The test discriminates the cognitive profile of MCI from Alzheimer's disease and depression and are highly sensitive to disease progression. A detailed description of the format of each test is listed below.

Reaction time - The participant must select and hold a button at the bottom of the screen. Circles are presented above (one for the simple mode, and five for the five-choice mode.) In each case, a yellow dot will appear in one of the circles, and the participant must react as soon as possible, releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared.

Paired associated learning - Boxes are displayed on the screen and are "opened" in a randomised order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time and the participant must select the box in which the pattern was originally located. If the participant makes an error, the boxes are opened in sequence again to remind the participant of the locations of the patterns. Increased difficulty levels can be used to test high-functioning, healthy individuals.

Spatial working memory - The test begins with a number of coloured squares (boxes) shown on the screen. The aim of this test is that by selecting the boxes and using a process of elimination, the participant should find one yellow 'token' in each of a number of boxes and use them to fill up an empty column on the right-hand side of the screen. Depending on the difficulty level used for this test, the number of boxes can be gradually increased until a maximum of 12 boxes are shown for the participants to search. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search

strategies.

Pattern recognition memory - The participant is presented with a series of visual patterns, one at a time, in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the participant is required to choose between a pattern they have already seen and a novel pattern. In this phase, the test patterns are presented in the reverse order to the original order of presentation. This is then repeated, with new patterns. The second recognition phase can be given either immediately or after a delay.

Delayed matching to sample - The participant is shown a complex visual pattern, that is both abstract and non-verbal (the sample), followed by four similar patterns, after a brief delay. The participant must select the pattern which exactly matches the sample. In some trials the sample and the choice patterns are shown simultaneously, in others there is a delay (of 0, 4 or 12 seconds) before the four choices appear.

Rapid visual information processing - A white box is shown in the centre of the screen, inside which digits from 2 to 9 appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8). When the participant sees the target sequence they must respond by selecting the button in the centre of the screen as quickly as possible. The level of difficulty varies with either one- or three-target sequences that the participant must watch for at the same time.

<u>Cognitive tasks</u>

Verbal fluency – This task requires participants to name as many objects from a certain category e.g. fruit, cities, and first names beginning with ‘‘A’’ and ‘‘M’’ within a 60 second time limit. The greater amount of correct words listed the greater the score.

Visual attention – This task is a type of “find the difference game”, in which participants have to verbally identify and pinpoint differences between two similar pictures. The difficulty of this task will increase by making the differences between pictures more difficult to identify. Images will be shown for a short period of time in which the more differences spotted the greater the score.

Auditory memory – This task will require participants to mentally count how many times the certain word e.g. diabetes is mentioned whilst the instructor reads a passage of text. The difficulty of this task will increase by increasing the length of text and how many time the word is mentioned. The greater number of words identified reflects a greater score.

Memory recall – This task will require participants to memorise a series of objects presented on a screen and then recall as many objects as possible after a short period of time. The difficulty of this task will increase by reducing the time the participant is exposed to the image. The greater number of objects recalled the greater the score.

Mental arithmetic – This task will reflect working memory and will require participants to count backwards in steps of seven, eight, or nine beginning alternately with different number e.g. 501, 502, 503 etc. Time taken to reach to a designated number will be recorded. A greater time taken will reflect a worse score.

The Stroop task - This task requires the participant to focus on one particular feature

	(language), while blocking out another (colour). Participants will be presented with a series of individual colour words presented on a screen in incongruent mode e.g. the word "red" written in a different colour. Participants will be required to name the word in which the colour was written. The time taken to name each colour word collectively correctly will be recorded. A greater time taken will reflect a worse score. <u>Evaluation questionnaire</u> The evaluation questionnaire will be utilised as a tool to gauge an idea of each participant's experience of the study participation. The questionnaire will consist of questions relating to the acceptability of all elements of the interventions and outcome measurements including time, duration, modality, intensity, delivery, and venue. A comment box will also be provided so that participants can provide further feedback or suggestions. The form should take no longer than 10 minutes to complete.	
	Approximate Start Date: 21/08/17	Approximate End Date: 22/12/17
6 Name of Principal Investigator or Supervisor	Samuel Cooke	
	Email address: scooke@lincoln.ac.uk	Telephone: 07731825915
7 Names of other researchers or student investigators involved	**1.** Dr. Ffion Curtis **2.** Dr. Kyla Pennington **3.** Dr. Mark F Smith	
8 Location(s) at which Project is to be carried out	1. Psychology Laboratory, Sarah Swift building, School of Psychology 2. Human performance laboratory, University of Lincoln Sports Centre, School of Sports and Exercise Science	

9 Statement of the ethical issues involved and how they are to be addressed –including a risk assessment of the project based on the vulnerability of participants, the extent to which it is likely to be harmful and whether there will be significant discomfort.	There are several risks associated with this study. All are disclosed below. Please see risk assessment and management document for further information. 1) Travel risks to and from location of research - Stairs/inclines - Traffic/train delay - Unfamiliar location - Complex directions to study location <u>Precautions taken by participant</u> - Travel with a companion

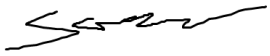
(This will normally cover such issues as whether the risks/adverse effects associated with the project have been dealt with and whether the benefits of research outweigh the risks)	- Plan routes to and from location - Be aware of alternate routes e.g. stairs/lift <u>Precautions taken by researcher</u> - Researcher to be aware of health and safety policies of study location and surrounding area - Provide contact details 2) Physical injury associated with physical exertion - Previous reoccurring injury - Family illness/past illness - Incorrect clothing causing injury <u>Precautions taken by participant</u> - Ensure they are wearing appropriate attire to perform exercise - Conduct sufficient warm up <u>Precautions taken by researcher</u> - Ensure all participants complete the PAR-Q form and are eligible to perform exercise - Be aware of actions to take in an event of an injury e.g. CPR, RICE, points of contact - Ensure participants conduct a sufficient warm up and cool down 3) Psychological/emotional fatigue - Complex cognitive tasks - Uncomfortable environment <u>Precautions taken by researcher</u> - Make sure the study location is a clean, friendly and approachable environment. - Allow time for participants to familiarise themselves with the study location - Ensure that participants can withdraw from the study at any point without question - Ensure participants are familiar with the protocol and procedure of each task before starting 4) Data collection/focus group discussion - Conflict between participants <u>Precautions taken by researcher</u> - Ensure there are researchers with experience and skill in group facilitation - Ensure the focus group location is a comfortable, friendly, and open environment 5) Disclosure of health or social care needs and sensitive information - Medication use - Previous medical history - Physical activity levels <u>Precautions taken by researcher</u> - Ensure all verbal and written information about research indicates researcher's response to disclosure

Ethical Approval from Other Bodies

10 Does this research require The approval of an external body ?	**Yes** ☐ **No** ☒
	If "Yes", please state which body:-
11 Has ethical approval already been obtained from that body ?	**Yes** ☐ **Please append documentary evidence to this form.** **No** ☒ **If "No", please state why not:-** N/A **Please note that any such approvals must be obtained and documented before the project begins.**

APPLICANT SIGNATURE

I hereby request ethical approval for the research as described above.
I certify that I have read the University's ETHICAL PRINCIPLES FOR CONDUCTING RESEARCH WITH HUMANS AND OTHER ANIMALS.



_____
_____13/07/17_____
Applicant Signature **Date**

_Samuel Cooke_____
PRINT NAME

Academic Support for Ethics

Academic support should be sought prior to submitting this form to the designated Ethics Committee within the Faculty
.

- Undergraduate / Postgraduate Taught application

Academic Member of staff nominated by the School/Department (consult your project tutor)

- Postgraduate Research Application

Director of Studies

I support the application for ethical approval

_____ __13/07/2017_____

Academic / Director of Studies Signature Date

Appendix G – Participant information sheet

Research project

"Walking, cognitive, and dual-task intervention in type 2 diabetes mellitus: A methodological development study"

Name of principal investigator: **Samuel Cooke**

Name of study co-investigators: **Dr. Ffion Curtis**

Dr. Kyla Pennington

Dr. Mark F Smith

This document provides information on:

1) The background and aim of the research project
2) The role of the researchers
3) Your role as a participant
4) Study protocol
5) Benefits
6) Risks
7) How the results will be used
8) Your rights

IMPORTANT

The purpose of this document is to assist you in making an informed decision about whether you wish to volunteer for this research project by promoting transparency in the research process.

1) Background and aims of the research

Ageing is naturally accompanied by a decline in the functioning of the human brain. It is suggested that type 2 diabetes mellitus (T2DM) is associated with an accelerated cognitive decline, significantly increasing the risk of dementia and Alzheimer's disease. Exercise and cognitive interventions have been shown to reduce the rate of decline in cognitive function in both healthy and diabetic populations. However, dual task interventions consisting of simultaneous exercise-cognitive tasks have shown to be superior in improving cognitive function compared to single task interventions in healthy populations. Yet, it remains unclear as to what effect a dual-task intervention may have upon cognitive function within a T2DM population. In order to conduct this investigation, an appropriate methodology needs to be developed. Therefore, the **aim** of this methods development study is to conduct a series of walking, cognitive, and dual-task sessions that will be used to inform the development of methods for interventions aiming to improving cognitive function in T2DM. In addition, this study will also pilot the cognitive outcome assessment measures.

2) The role of the researchers

The researcher (Samuel Cooke) will be responsible for conducting and overseeing all stages of this research project. Sam will be your main study contact and will assist you in relation to any questions or issues you may have. During each visit, he will explain all the project details so that you feel comfortable with knowing exactly what will be required. The researcher will also assist you with the completion of any documentation and answer any questions you may have in relation to the project. Whilst our research interest is to develop interventions for improving cognitive function in T2DM, your health and safety is of primary importance to us and takes precedence over our

research interests. In relation to this, you will be able to ask questions and inform us about any issues during the research project in which we will also provide you with contact details for 2 members of the research team should you have any concerns. The researcher encourages you to ask questions at any point should you feel uncomfortable or have questions related to the project.

3) Your role

We are very grateful should you choose to take part in this research project and we will treat you with respect at all times and try our best to explain everything to you so that you have an enjoyable experience. Whilst we need to ensure the quality of our work, we also aim to create a friendly and positive environment during your visits. Your role in this research project is to attend eight sessions over the space of four weeks (two sessions per week) held at the University of Lincoln. As part of the first week you will be required to participate in two treadmill walking sessions. Don't worry if you haven't used a treadmill before, we will provide full instructions and guided support. During the second week you will be required to participate in two cognitive task sessions such as recalling memorised pictures and performing mental math tasks and in the third week you will be required to participate in two dual task sessions (walking and cognitive task together). The fourth and final week you will be invited to complete a computer based cognitive test alongside completing an evaluation questionnaire during the first session as well as take part in a group discussion followed by a questionnaire in the second session. Details of each session are outlined below in the study protocol.

4) Study protocol

As part of the project you are required to attend the University of Lincoln twice a week for a period of four weeks. What you will be required to do is outlined below. It is important to remember that you can ask questions about the research at any point during this project.

Preliminary study visit

Prior to starting week 1, you will be invited to take part in a pre-study familiarisation visit. The purpose of this visit is to obtain informed consent from you and assist you in reviewing and completing the physical activity readiness questionnaire (PAR-Q) and mini mental state examination (MMSE) (tools that help us decide whether you are eligible to participate in this study). You will also be familiarised with the procedures and equipment used in each type of session e.g. treadmill walking, cognitive tasks, using the Borg scale (a scale that helps to determine how fast you walk) etc. In addition, you will receive advice on the appropriate attire to wear during the walking visits along.

Week 1 – exercise phase (Sessions 1 & 2)

Session 1

Initially you will be required to re-read the participant information sheet or confirm that you are clear and understand the study protocol. At this point any outstanding questions you would like answered may be asked prior to treadmill walking. Subsequently, treadmill walking will begin with you completing a 5-minute warm up performed at a self-selected intensity. Following this, you will then treadmill walk at a low intensity for 40 minutes. The session will then be followed by a 5-minute cool down period performed at a self-selected intensity.

Session 2

Session 2 will follow the same procedure as session 1.

Week 2 – cognitive phase (Sessions 3 & 4)

Session 3

The first cognitive session will require you to perform a series of different cognitive tasks. Each cognitive task will be practiced for approximately 5-10 minutes with the session duration lasting approximately 40 minutes in duration. It is important to note that not all tasks listed below will be used in one session but will be split across session 3 and 4. The difficulty will remain low for the duration of this session. The following cognitive tasks will be practiced;

1) **Verbal fluency:** whereby you are required to name as many words from a category as possible e.g. fruits, capital cities etc. in a 60 second period.
2) **Visual attention:** Whereby you are required to spot the differences between two similar pictures.
3) **Auditory memory training:** whereby you are required to mentally count how many times a word was mentioned whilst the instructor reads a short text or long text.
4) **Memory recall:** whereby you are required to memorize a list of items in which you then recall the items on the list immediately or following a delayed period.
5) **Mental arithmetic task:** whereby you will be required to count back in sevens, eights, or nines from alternating numbers
6) **The Stroop task:** whereby you are to name the colour in which a word is printed, ignoring the word itself.

Session 4

Session 4 will follow the same protocol as session 3, with the exception that the difficulty of some cognitive tasks will increase throughout the session.

Week 3 – (Sessions 5 & 6)

Session 5

Week 5, you will be required to complete the dual-task phase. Session 5 will follow the same procedure as week 1 with the exception that you will perform combined walking-cognitive activities consisting of the same activities performed in weeks 1 & 2 (E.g. treadmill walking whilst performing a memory recall task). The difficulty of each cognitive task will remain low in this session.

Session 6

Session 6 will follow a similar protocol to session 5 with the exception that the difficulty of certain cognitive tasks will increase throughout the session.

Week 4 – (Sessions 7 & 8)

Session 7

As part of the final phase of this study, you will be required to conduct a computerised cognitive test battery that will assess your cognitive function. The test battery is

performed on a specialist touch screen laptop and will take no longer than 35-45 minutes. The test battery includes tests such as:

- Motor screening task
- Reaction time
- Paired associated learning
- Spatial working memory
- Pattern recognition memory
- Delayed matching to sample
- Rapid visual information processing

In addition, each participant will also be required to complete an evaluation questionnaire regarding their thoughts and experiences of the study at the end of this session.

Session 8

The final session of this research project will require you to attend a focus group with the aim of discussing your thoughts and experiences of each element of study, walking, cognitive, and dual-task, as well as the computerised neuropsychological test battery. The discussion will be guided using prompts and open ended questions and recorded and transcribed. The group discussion will last approximately 1-2 hours in duration. Once you have completed this session, the project will be complete.

6) Benefits

You will experience and contribute towards innovative and novel research that may be used to improve cognitive function in a type 2 diabetes mellitus.

7) Risk

For all individuals, there are some risks associated with exercise, however, this is minimized by the use of a screening tool to identify any risk factors that could require you to get medical approval before taking part (GP phone call or appointment). In

addition to this, the exercise will be performed at a low to moderate intensity and in the form of walking, a modality that is part of our usual daily activities. Furthermore, you will be advised on appropriate attire to wear whilst performing walking exercise which if adhered to will also help minimise the risk of injury.

8) How the data / research will be used

If you do decide to take part in this study only the research team will have access to information collected during the study. If you take part you will be agreeing that we can use data collected from you for the purpose of research. This may include written reports for publication, however, all data will be anonymised. That means you will not be named in any material, and it will not be possible to identify you.

8) Your rights

IMPORTANT: Your right as a voluntary participant is that you are **free to enter or withdraw from the study at any time**. This simply means that you are in full control of the part you play in informing the research and what anonymous information is used in its final reporting.

9) Protection to your privacy

Your identity will not be disclosed in any written transcripts, notes or associated documentation that informs the research and its findings. Furthermore, any personal information about you will remain confidential according to the guidelines of the Data Protection Act (1998).

10) Data storage

Personal data, research data and the linking code will be stored in separate locations. When stored electronically, this will include using encrypted digital files within password protected folders and storage media. Personal information shall be stored separately to research data and will be kept secure, and maintained. Physical storage may include (but not limited to) locked filing cabinets with restricted access/locked office. In

accordance with the University of Lincoln's policy, data will be kept intact for five years at least and will be deleted or destroyed in accordance with all legal, ethical, research funder and organisational requirements and with particular concern for confidentiality and security.

11) Guidance regarding withdrawal

Participants shall be withdrawn from study if consent is withdrawn – it shall be noted that data should not/cannot be destroyed, as it should be possible to recreate a participant's participation up to the point of withdrawal. Participants should also be made aware that withdrawal will not affect their future care/employment/involvement in future studies. Participant should also be made aware that data may still be used in the final analysis where data analysis has already taken place.

12) Contact details

If you require further information or have any outstanding queries, feel free to contact the principal investigator or a co-investigator.

Samuel Cooke
Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS
Email: scooke@lincoln.ac.uk

Dr. Ffion Curtis
Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS
Email: fcurtis@lincoln.ac.uk

Dr. Kyla Pennington

School of Psychology, University of Lincoln, Brayford pool, Lincoln, LN6 7TS
Email: kpennington@lincol.ac.uk

Dr. Mark F Smith

School of Sports and Exercise Science, University of Lincoln, Brayford pool,

Lincoln, LN6 7TS Email: mfsmith@lincoln.ac.uk

Appendix H – Informed consent sheet

UNIVERSITY OF LINCOLN

CONSENT FORM

Title of Project:

"Walking, cognitive, and dual-task interventions in type 2 diabetes mellitus: A methodological development study"

Principal Investigators:
Sam Cooke scooke@lincoln.ac.uk
Dr. Ffion Curtis fcurtis@lincoln.ac.uk
Participant Identification Number:

Please tick the appropriate box for each question / statement.

	YES	NO
1. I confirm that I have read and understand the information sheet related to this study. I have had the opportunity to consider this information, ask questions and have my questions answered satisfactorily.	☐	☐
2. I understand that my participation is voluntary and that I am free to withdraw from this study at any time, without giving reason, and without my medical care or legal rights being affected.	☐	☐
3. I understand that the data collected in this project will not be used for commercial purposes. I agree that the principal and co-investigators of this study may use my data anonymously in other research projects with the purpose of answering new research questions.	☐	☐
4. I agree to take part in the above study.	☐	☐

CONSENT FORM
(Continued)

Participant

Name: _____ **Date:** _____ **Signature:** ……..____

Researcher taking consent

Name: _____ **Date:** _____ **Signature:** ……..____

If you have any ethical concerns or complaints please contact the School of Psychology Ethics Procedures (SOPREC)

zmead@lincoln.ac.uk

01522 835510

END OF DOCUMENT

Appendix I – Study recruitment poster

UNIVERSITY OF LINCOLN
LINCOLN INSTITUTE FOR HEALTH

Do you have type 2 diabetes mellitus?

If so.....

We are currently recruiting individuals who are aged **25-69 years**, diagnosed with **type 2 diabetes mellitus**, and work/study at the **University of Lincoln** to participate in a methodological development study.

The aim of this research is to develop walking, cognitive, and dual-task interventions for improving cognitive function in type 2 diabetes mellitus.

What does this study involve?

You will be invited to attend 8 x 40 minute sessions over a 4 week period.

- Week one – 2 x treadmill walking sessions
- Week two – 2 x brain training sessions
- Week three – 2 x combined treadmill walking + brain training sessions
- Week four – 1 x touchscreen test battery + 1 x discussion session

What are the benefits?

You will experience and contribute towards innovative and novel research that may be used to improve cognitive function in a type 2 diabetes mellitus.

Interested? Please contact Mr. Samuel Cooke

Email: scooke@lincoln.ac.uk **Tel:** 07733182591

Appendix J – Physical activity readiness questionnaire

Forename:_____
Surname:_____
Date of Birth:_____ **Contact Number:**_____
Student Number:_____

Please delay exercise if;

- You are not feeling well because of a temporary illness such as a cold or fever - wait until you feel better
- If you are or may be pregnant, talk with your doctor before you start becoming more active.
- Please consult a Doctor if you develop a condition that may be aggravated by exercise

Please read the questions below carefully and answer each one honestly (check YES or NO)	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition **OR** high blood pressure?		
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?		
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).		
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?		
5) Are you currently taking prescribed medications for a medical condition?		
6) Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer **NO** if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.		
7) Has your doctor ever said that you should only do medically supervised physical activity?		

If you checked YES to any of the above, please provide details:
Please provide the name, address and number of your doctor in the space below

Emergency Contact Name & Address:

Emergency Contact Number:

Emergency Contact Relationship:

Further information requested

……..

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.....

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Outcome

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.....

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No action required Doctors letter requested

Once doctor's letter is presented please copy and attach to form.

Staff

Signature_____

Signature: **Date:**

Appendix K– Mini-mental state examination

Patient's Name:_____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)
30		TOTAL

Appendix L – Evaluation questionnaire

UNIVERSITY OF LINCOLN

Evaluation questionnaire

Title of Project:

"Walking, cognitive, and dual-task interventions in type 2 diabetes mellitus: A methodological development study"

Principal Investigators:
Sam Cooke scooke@lincoln.ac.uk
Dr. Ffion Curtis fcurtis@lincoln.ac.uk
Participant Identification Number:

Please circle the appropriate number for each question

Walking sessions

Q1. Overall how difficult did you find the walking sessions?	1	2	3	4	5	6	7	8	9	10
Q2. How difficult did you find the type of exercise (walking)?	1	2	3	4	5	6	7	8	9	10
Q3. How did you find the duration of the session?	1	2	3	4	5	6	7	8	9	10
Q4. How difficult did you find the intensity of walking?	1	2	3	4	5	6	7	8	9	10
Q5. Was the frequency of walking sessions appropriate?	1	2	3	4	5	6	7	8	9	10

Cognitive sessions

Q6. Overall how difficult did you find the cognitive sessions?	1	2	3	4	5	6	7	8	9	10
Q7. How difficult did you find the type of cognitive tasks?	1	2	3	4	5	6	7	8	9	10
Q8. How did you find the duration of the session?	1	2	3	4	5	6	7	8	9	10
Q9. How difficult did you find the complexity of tasks?	1	2	3	4	5	6	7	8	9	10
Q10. Was the frequency of cognitive sessions appropriate?	1	2	3	4	5	6	7	8	9	10

Dual-task sessions

Q12. Overall how difficult did you find the dual-task sessions?	1	2	3	4	5	6	7	8	9	10
Q12. How difficult did you find combined training?	1	2	3	4	5	6	7	8	9	10
Q13. How did you find the duration of the session?	1	2	3	4	5	6	7	8	9	10
Q14. How difficult did you find the intensity of tasks?	1	2	3	4	5	6	7	8	9	10

Cognitive test battery

Q16. How difficult did you find the cognitive test battery? 1 2 3 4 5 6 7 8 9 10

Q17. Was the touch screen laptop easy to use? 1 2 3 4 5 6 7 8 9 10

Q18. Was the test battery clear and easy to follow? 1 2 3 4 5 6 7 8 9 10

Q19. How did you find the duration of the cognitive test battery? 1 2 3 4 5 6 7 8 9 10

Study location

Q20. How difficult was it to travel to the study location? 1 2 3 4 5 6 7 8 9 10

Q21. How difficult was it to access the study location? 1 2 3 4 5 6 7 8 9 10

Q22. How comfortable was the study location? 1 2 3 4 5 6 7 8 9 10

Q23. How difficult was it use the study equipment? 1 2 3 4 5 6 7 8 9 10

Study investigators

Q24. How approachable were the study investigators? 1 2 3 4 5 6 7 8 9 10

Q25. Was the protocol for each session explained clearly? 1 2 3 4 5 6 7 8 9 10

Q26. Were clear instruction given for using study equipment? 1 2 3 4 5 6 7 8 9 10

Q27. Was the study conducted in a professional manner? 1 2 3 4 5 6 7 8 9 10

Any further comments or suggestions please leave in the box below.

Appendix M – Study debrief form

Study Debrief form

Developing exercise, cognitive, and dual-task interventions for improving cognitive function in type 2 diabetes mellitus

The researchers would like to thank you for your participation in this research project. This study aimed to conduct a series of walking, cognitive, and dual-task sessions that would be used to develop methods for interventions aiming to improving brain function in type 2 diabetes mellitus (T2DM). Previous evidence has shown both exercise and cognitive interventions to be effective in improving brain function in both healthy and diabetic people. Growing evidence within healthy people suggest that dual-task interventions (physical and cognitive activities together - e.g. treadmill walking whist performing a cognitive task) may be better for improving brain function compared to single task interventions (e.g just treadmill walking). However, we still don't know what effect a dual-task intervention may have upon brain function in people with T2DM.

How was this tested?
In this study, you were asked to attend eight sessions over a four week period where you to took part in walking, cognitive, and dual-task activities as well as completing a computerised test. You performed the same activities for the same amount of time at the same intensity/difficulty as every other participant. You were then asked to complete an evaluation questionnaire regarding your thoughts and experiences of the study. Finally, you were invited to discuss your experience of each intervention and computerised test as part of a focus discussion group following prompts and open-ended questions. The discussion was recorded and transcribed.

Hypotheses and main questions:
We are interested in investigating the acceptability (your experience of these tasks) of exercise, cognitive, and dual-task interventions as well as a computerised test. The feedback from this study will help us develop appropriate interventions for improving brain function for people with T2DM.

Why is this important to study?

The number of people with T2DM in the UK is increasing as are the associated complications such as heart disease, stroke, nerve damage, eye damage, and kidney disease and cognitive impairment. Ultimately, diabetes-induced cognitive impairment considerably increases one's risk of developing severe cognitive complications such dementia and Alzheimer's disease imposing a significant burden for both the individual and their care provider. Cognitive impairment, however, has not been targeted by current UK management strategies set out for T2DM. The current study is important as it may contribute to the development of novel interventions and thus management/treatment strategies for preventing/improving cognitive impairment within T2DM.

What if I want to know more?

If you are interested in learning more about T2DM and cognitive function and how exercise and cognitive training may influence this relationship please see below for further information.

1) https://www.diabetes.org.uk/Documents/Position%20statements/DiabetesUK_Facts_Stats_Oct16.pdf

2) Kodl, C.T. & Seaquist, E.R. (2008) Cognitive Dysfunction and Diabetes Mellitus. Endocrine Reviews, 4(29) 494-511.

3) Gomez-Pinilla, F. & Hillman, C. (2013) The Influence of Exercise on Cognitive Abilities. Comprehensive Physiology, 1(3) 403-428.

4) Mowszowski, L., Lampit, A., Walton, C.C. & Naismith, S.L. (2016) Strategy-Based Cognitive Training for Improving Executive Functions in Older Adults: a Systematic Review. *Neuropsychological Review*, 3(26) 252-270.

Thank you again for your participation in this study, if you have any further questions or queries regarding this study please find contact details below.

Samuel Cooke
Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS Email:

Dr. Ffion Curtis
Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS Email: fcurtis@lincoln.ac.uk

Dr. Kyla Pennington

School of Psychology, University of Lincoln, Brayford pool, Lincoln, LN6 7TS
Email: kpennington@lincol.ac.uk

Dr. Mark F Smith
School of Sports and Exercise Science, University of Lincoln, Brayford pool, Lincoln, LN6 7TS Email: mfsmith@lincoln.ac.uk

Appendix N – IRAS protocol

PROTOCOL Title: Investigating the effects of a computerised cognitive training intervention on cognitive function in type 2 diabetes mellitus. Short title: Effect of cognitive training on cognition in type 2 diabetes Protocol Version 1.1 Date 31st May 2018	
IRAS Project ID	227672
Registration ID	N/A
Sponsor	University of Lincoln
Sponsor ID	180201
Funder	PhD studentship through the University of Lincoln funded by the Doctoral Training Alliance (DTA)

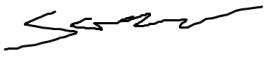
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement(s).

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:  Date: 31/05/18

Name: Samuel Cooke

STUDY/TRIAL CONTACTS

Chief Investigator	Dr Ffion Curtis Lincoln Institute for Health Bridge House, BH2206 Research Fellow/PhD supervisor University of Lincoln Brayford Pool Lincoln LN6 7TS 01522 835732 fcurtis@lincoln.ac.uk
Sponsor	Professor Sara Owen University of Lincoln Brayford Pool Lincoln LN6 7TS 01522 835512 sowen@lincoln.ac.uk
Collaborators/Co-Investigators/Protocol Contributors	Samuel Cooke Lincoln Institute for Health Bridge House, BH2212 University of Lincoln Brayford Pool Lincoln LN6 7TS UoL job title: PhD student Phone: 07731825915 Email: scooke@lincoln.ac.uk Dr Kyla Pennington Senior lecturer/researcher University of Lincoln Brayford Pool Lincoln LN6 7TS 01522 886199 kpennington@lincoln.ac.uk

FUNDER DETAILS

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
(Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	Doctoral Training Alliance University Alliance 49 Whitehall London SW1A2BX 02078392757 Infor@unialliance.ac.uk

Abbreviations

ANOVA = Analysis of Variance

BDNF = Brain-Derived Neurotrophic Factor

BMI = Body Mass Index

CANTAB = Cambridge Neuropsychological Test Automated Battery

CCT = Computerised Cognitive Training

CI = Chief Investigator

ELISA = Enzyme-linked Immunosorbent Assay

GCP = Good Clinical Practice

HbA1c = Glycated Haemoglobin

HRA = Health Research Authority

ICF = Informed Consent Form

MMSE = Mini-Mental State Examination

R&D = National Health Service Research & Development

PIS = Participant Information Sheet

RCT = Randomised Controlled Trial

T2DM = Type 2 Diabetes Mellitus

REC = Research Ethics Committee

SSB = Sarah Swift Building

UoL = University of Lincoln

STUDY SUMMARY

Study Title	Investigating the effect of a computerised cognitive training intervention on cognitive function in type 2 diabetes.
Study Design	Feasibility/Pilot study/Randomised controlled trial (RTC)
Study Participants	Type 2 diabetes mellitus (T2DM)
Eligibility Criteria	Male or female Age 45+ Diagnosed with T2DM (identified through GP register or self-declared) No cognitive impairments as indicated by the mini-mental state examination (MMSE) (23 or below) No literacy or communication impairments No comorbidities that may affect computer use e.g. peripheral neuropathy, glaucoma No recent change (within the last 6 months) in drugs treatment e.g. medication to insulin or type of insulin treatment Have not undertaken any recent (within the last 3 months) structured cognitive training Can speak English.
Planned Sample Size	Total sample n=70 Cognitive intervention arm n=35 Control arm n=35
Study Duration	June 2018 – June 2019
Objectives	Primary - To investigate the feasibility of a RCT examining the effect of a CCT intervention on cognitive function in T2DM.
Outcomes	Primary outcome Recruitment rate, adherence, acceptability, motivation, qualitative data from semi-structured interviews Secondary outcome Cognitive function BDNF Demographic outcomes Age, gender, body mass index (BMI), education status,

	glycated haemoglobin (HbA1c)
`Data Analysis	Differences in cognitive scores will be measured using a multiple analysis of variance (ANOVA). Serum levels of BDNF will be batch analysed using enzyme-linked immunosorbent assay (ELISA) and statistically analysed using a multiple regression.

KEY WORDS

T2DM

Cognitive function

CCT

BDNF

HbA1c

STUDY MANAGEMENT

ROLE OF STUDY SPONSOR AND FUNDER

The funder of the study is the Doctoral Training Alliance and the sponsor is the University of Lincoln (UoL). The Chief Investigator (CI) has overall responsibility for the study and shall oversee all study management. The funder does not have any role/responsibilities or final decisions regarding the study design, conducting of experiments, data analysis, interpretation, manuscript writing, or dissemination of results.

STUDY MANAGEMENT COMMITTEES

Study /Management Group

The Study Management Group shall meet monthly to ensure all practical details of the study are progressing well and working well and everyone within the study understands them.

STUDY BACKGROUND and RATIONALE

T2DM is a chronic metabolic disorder characterised by hyperglycaemia and precipitated as a result of abnormalities in glucose metabolism[1-3]. Approximately 3.5 million individuals are diagnosed with diabetes in the UK, of which 90% of cases are attributed to T2DM[4]. In contrast to type 1 diabetes mellitus, the onset of T2DM typically manifests during later adulthood and is largely a result of the dynamic interplay between lifestyle and genetics factors[5-8]. T2DM is strongly associated with the development of both microvascular and macrovascular complications, including retinopathy, nephropathy, peripheral neuropathy, cardiovascular disease and cerebrovascular disease, significantly increasing the risk of tissue and end organ damage[9-11]. In addition to these well recognised microvascular and macrovascular complications, accumulating evidence suggests that T2DM may also have a detrimental impact upon cognitive function[12-14].

Several longitudinal studies examining the impact of diabetes upon cognitive function suggest that the rate of cognitive decline in diabetes exceeds that of healthy aging by a factor of 1.5 – 2 fold[15-20]. In agreement, imaging studies have also observed an accelerated cognitive decline in T2DM individuals in combination with an enhanced deterioration of several structural correlates including brain volume, neuronal count, and vasculature integrity[21-23]. The underlying pathophysiology of cognitive dysfunction in T2DM is complex and remains poorly understood. Several mechanistic studies have highlighted the role of hyperglycaemia, insulin dysfunction, inflammation, and both microvascular and macrovascular complications in provoking this enhanced deterioration in cognition[24-26]. Consequently, it is suggested that individuals with T2DM are at a significantly greater risk of developing severe cognitive dysfunction such as dementia or Alzheimer's disease compared to non-diabetic counterparts[27, 28].

Regarding strategies for improving cognitive function, cognitive training interventions have been shown to be effective in improving cognitive function in healthy aging cohorts[29-31], with evidence to suggest that CCT is more effective and less labour intensive than more traditional pencil-to-paper training approaches[31]. Although the use of CCT to target cognitive decline in later adulthood is still considered an emerging area, the beneficial effects of such interventions have been documented across several cognitive domains including, memory[32, 33], attention[34, 35], executive function[36, 37], speed processing[38, 39], visual spatial abilities[40, 41] and global cognitive function[42, 43]. However, evidence regarding the effect of cognitive training

interventions on cognitive function in T2DM is limited, with only one intervention being conducted showing positive improvements across various domains of memory[44]. It is therefore important to further explore the effect of cognitive training interventions as it is still unclear as to what kind of effect these intervention may have in a T2DM population.

Furthermore, a mechanism by which cognitive training is suggested to facilitate improvements in cognitive function is through elevations in a growth factor named BDNF. BDNF plays a crucial role in brain development, facilitating synaptic plasticity and neurogenesis[45-48]. Changes in BDNF levels are known to affect the development and regulation of neural circuits and brain function and is found to be positively correlated with cognitive ability[49, 50]. Previous evidence has shown BDNF levels to increase in response to cognitively stimulating tasks in both healthy cohorts[51] and individuals with mild cognitive impairment[52, 53]. However, it is unknown as to what effect a cognitive training intervention may have on levels of BDNF in a T2DM population.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

Cognitive decline and dementia represent very important public health problems that impact the ability to maintain social function and independent living. T2DM is associated with an accelerated cognitive decline increasing the risk of dementia and Alzheimer's disease. Whilst cognitive training has been shown to be effective in reducing the rate of cognitive decline and improving cognitive function in healthy ageing cohorts, evidence is limited within a T2DM population. The purpose of this research is to further explore the effects of a CCT intervention on cognitive function in a T2DM population.

PRIMARY OBJECTIVE

To investigate the feasibility of a RCT examining the effect of a CCT intervention on cognitive function in T2DM.

OUTCOME MEASURES/ENDPOINTS

PRIMARY OUTCOME MEASURE/ENDPOINT

Feasibility outcomes

Feasibility outcomes will include a range of measures to capture data crucial to determining feasibility and planning for a full trial.

Recruitment rate and method: we will record the number of patients identified with T2DM, number of individuals consenting to be contacted, number of indivduals suitable for CCT, number of individuals contacted by telephone/email, and number of individuals enrolled into the study.

Uptake, adherence and maintenance: we will record the number of individuals attending the first session compared to number of individuals invited as well as the number of cognitive training sessions individuals attended.

Intervention acceotability assessed using semi structured interviews and evaqluation questionnaires.

Semi-structured interviews: Telephone interviews will be conducted with participants and will seek to understand the participant's views on the acceptability of each component of this intervention e.g. programme length, duration of tasks, complexity of tasks, and frequency of tasks, venous blood extraction, computerised cognitive equipment etc. In addition, interviews will seek to understand the views of participant's who received usual care. A semi-structured interview guide for these interviews will be designed. All interviews will be audio recorded and transcribed verbatim. NVivo software will be used to analyse the anonymised transcripts, using thematic analysis to inductively code the data. To ensure rigour and consistency in coding, a subset of the transcripts (10%) will be coded independently by a separate researcher. Identified themes will be discussed between the research team with the aim to enhance credibility and transparency of the analytical process.

Motivation: The motivation of individuals will be assessed at the beginning of each CCT session as part of the cognitive training battery using the visual analogue scales

SECONDARY ENDPOINTS/OUTCOMES

Cognition: Cognitive function will be measured using a selection of neuropsychological tests derived from Cambridge Neuropsychological Test Automated Battery (CANTAB) developed by Cambridge Cognition. The test battery will be conducted via a computer based cognitive assessment system using a touch screen computer. T2DM is a risk factor for dementia and Alzheimer's disease, therefore participants will be tested using a prodromal Alzheimer's/mild cognitive impairment test battery pre-specified by CANTAB (Appendix A). This test battery has been shown to be highly sensitive to cognitive impairments showing clinically meaningful outcomes associated with impaired day to day function. Participants will complete the cognitive test battery at two time points, baseline and post-intervention

BDNF: BDNF is a protein that plays a crucial role in brain development, facilitating synaptic plasticity and neurogenesis. Changes in BDNF levels are known to affect the development and regulation of neural circuits and brain function and is found to be positively correlated with cognitive ability. Previous evidence has shown BDNF levels to increase in response to cognitively stimulating tasks. Thus, measuring the changes in BDNF may provide a good indication of the impact of the interventions upon changes in brain health. Venous blood samples will be extracted at two time points, pre-intervention and post-intervention. Serum blood samples will be extracted from participants, centrifuged, and stored frozen at −80 °. BDNF levels will be batch analysed using ELISA in which a detailed description of procedures can be found at http://www.biosensis.com/documents/ELISA-kit-protocols/BEK-2211-2P_as_at_Oct2013_protocol.pdf.

HbA1c: HbA1c is a diagnostic test for diabetes mellitus which provides an indication of an individual's average blood glucose levels over the previous two to three months. There is strong evidence to suggest that the fluctuation of blood glucose levels per se is closely associated with cognitive impairment and the incidence of dementia in T2DM. Thus, measuring HbA1c may provide the researcher with an indication of the association between cognitive ability and blood glucose levels. A simple finger prick test will be performed in which samples will be analysed using a portable HbA1c monitoring device (HemoCue HbA1c 501 Analyser), details of the procedure can be found at https://www.hemocue.com/-/media/hemocue-images/hemocuedotcom-images/product-images/hba1c/hba1c-brochure.pdf?la=en&la=en.

Other secondary outcome measurements will include population characteristics that will help describe the population such as such as age, gender, BMI, education status.

TABLE OF ENDPOINTS/OUTCOMES

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objectives	Recruitment rate Adherence rate Acceptability Motivation (visual analogue scales) Semi-structured interviews Evaluation questionnaires	Continuously (recruitment rate, adherence rate, motivation) Post intervention (Questionniares and semi-structured interviews)
Secondary Objectives	Cognitive function BDNF	Pre-intervention and post intervention
Demographic outcomes	Age Gender BMI Education status HbA1c	Pre-intervention

STUDY DESIGN

A RCT study design will be used to investigate the effect of a CCT intervention on cognitive function in T2DM. Recruitment will be conducted from June 2018 – April 2019 with data collection being conducted from June 2018 – June 2019. A random number generator will be used to allocate eligible study participants into either a CCT group or control group. Primary and secondary outcome measurements will be recorded pre-intervention and post-intervention.

DATA ANALYSIS

Analysis of cognitive data will take place in the psychology laboratories, Sarah Swift Building (SSB), UoL and will be performed using CANTAB in which collected data at baseline and post-intervention will be transferred and stored in a Microsoft excel spread sheet for statistical analysis. Blood samples will be analysed in a wet laboratory, SSB, UoL using a batch ELISA technique to identify levels of BDNF. Levels of BDNF will be recorded, transferred and stored in a Microsoft excel spread sheet document for statistical analysis. Statistical analysis of the differences between the experimental and control group and baseline and post-intervention will be tested using a one-way ANOVA. The level of statistical significance will be set at $P < 0.05$ and will be determined by performing a priori power analysis. All statistical tests will be performed using SPSS (IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.) All data and statistical analysis will be conducted by the CI.

STUDY SETTING

Baseline and post-intervention assessment visits will take place in the CANTAB laboratory, SSB, UoL. The cognitive intervention arm will be conducted in either the CANTAB laboratory, SSB, UoL or in the participant's home. Blood samples collected at baseline and post intervention for the purpose of measuring BDNF levels will be collected in the CANTAB laboratory, SSB, UoL and subsequently frozen and stored in a wet laboratory located in the SSB, UoL.

SELECTION OF PARTICIPANTS

ELIGIBILITY CRITERIA

Inclusion Criteria

Individuals will be recruited to participate in this project if they are male or female aged 45+ and diagnosed with T2DM (Identified through GP registers or self-declared).

Exclusion Criteria

Individuals will be excluded from participating in this project if they are diagnosed with pre-diabetes or type 1 diabetes mellitus, are below the age of 45 years, are identified as cognitively impaired as indicated using the MMSE (cut off 23 or below), are in need of any arrangements for any special literacy or communication skills, have any co-morbidities that may affect computer use e.g. peripheral neuropathy or glaucoma, have recently (within the last 6 months) changed diabetes treatment e.g. medication to insulin, or type of insulin treatment, have recently undertaken (within the last 3 months) a structured cognitive training regime, and do not speak English.

Size of sample

The size of sample was determined using previous evidence[54] that recommends an external pilot study that uses standard deviation for continuous outcomes should have at least 70 subjects (35 per group).

Sampling technique

Initially, patients will be recruited using a volunteer/self-selecting approach through primary and secondary healthcare settings in which study packs will be disseminated to potential participants at local diabetes support clinics and GP practices. Potential participants may also volunteer/self-select in response to posters, flyers, and emails that are sent or advertised in local GPs and at the University of Lincoln. In addition, a snowball sampling technique will also be used in which existing study participants/nurses/GPs may recruit other potential participants through word of mouth. Purposive sampling will be used as individuals with diagnosed with T2DM are the population of interest. This sampling strategy will be applied as this is the most effective route in recruiting individuals diagnosed with T2DM.

RECRUITMENT

GP practices will screen databases to identify potential eligible participants. Study information packs will be written and packed into stamped envelopes and distributed to local practices. The practices will then forward the study information packs to patients on their registers who meet the inclusion criteria of the study. The information packs will include details of the research project and contact details for staff involved with this project. If recruitment uptake is slow then alternative recruitment pathways may be employed. This will

include the dissemination of study information packs via local diabetic community and United Lincolnshire Hospitals NHS Trust clinics.

Other recruitment methods will include the dissemination of posters and flyers in local GP practices, community centres, community boards, diabetic clinics, and at the UoL Brayford pool campus. In addition, advertisement emails will be sent to both staff and student mailing lists at the University of Lincoln along with poster invitations advertised on the staff and student news feeds. Invitation emails containing study information will also be sent to both the UoL and local Diabetes Support Groups. Recruitment will also take place externally through word of mouth e.g. friends and family.

CONSENT

Written consent will be received from all participants. Initially, potential participants will receive study information packs containing a study information sheet. If interested in taking part, potential participants will complete and return the expression of interest form attached to the participant information sheet (PIS) and return it to the CI. The CI will then contact the potential participant and obtain verbal consent whilst answering any questions they may have regarding the study.

Potential participants will then be invited to a screening/enrolment visit. Likewise, potential participants who express interest through other recruitment pathways e.g. posters/flyers, website advertisement, emails etc will also be invited to a screening/enrolment visit. During the screening/enrolment visit, written informed consent will be taken from each potential participant before they undergo any study interventions, including cognitive pre-screening. The CI will also explain the details of the study, including the study objectives and possible risks, and provide a PIS (and any other study related literature) ensuring that the participant has sufficient time to consider participating or not.

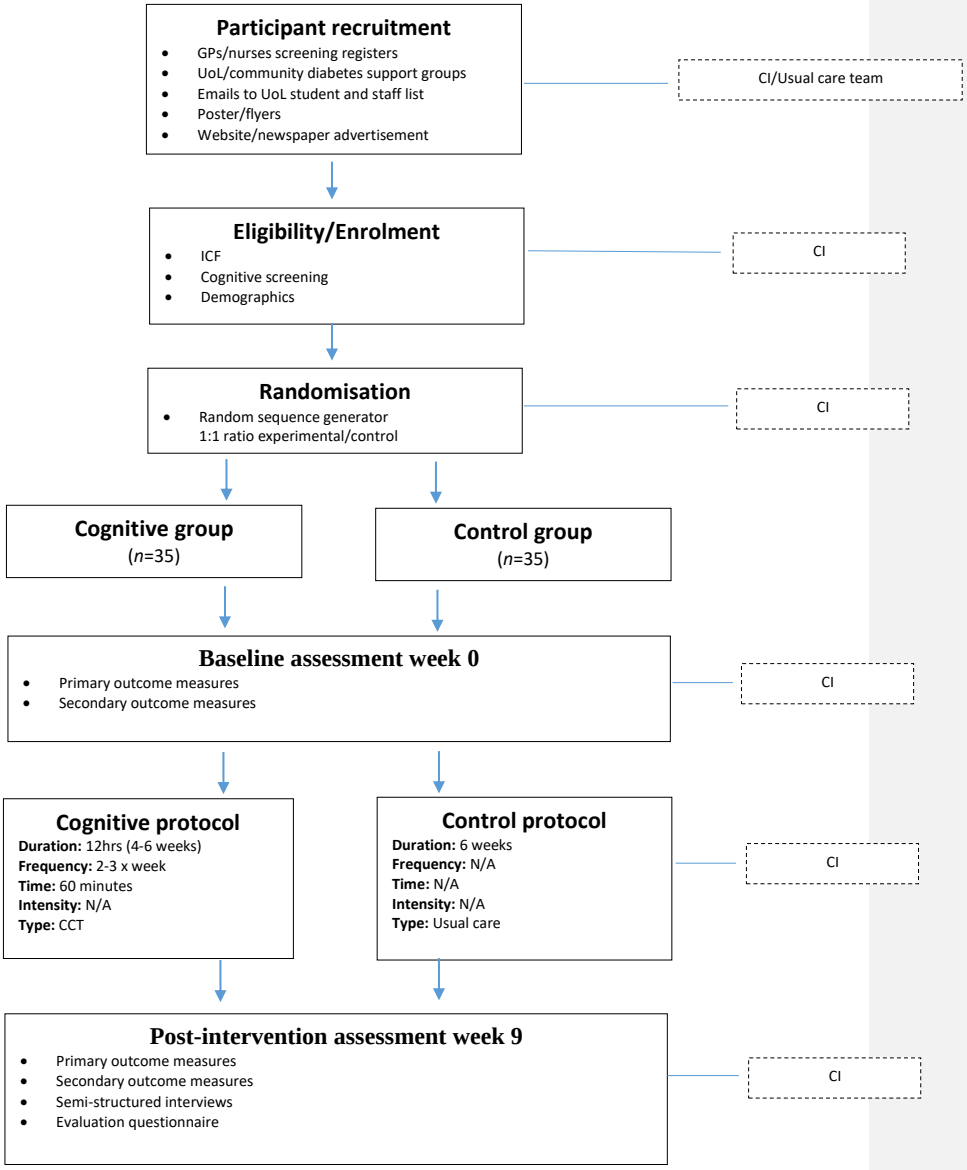
Opportunity will be given to the participant to ask any further questions they may have concerning study participation.

The process for obtaining participant informed consent will be in accordance with the Research Ethics Committee (REC) guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The CI or their nominee and the participant shall both sign and date the informed consent form (ICF) before the person can participate in the study.

One copy of the ICF will be kept by the participant and one will be kept by the CI. Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended ICF which will be signed by the participant.

STUDY PROCEDURES/REGIMEN

STUDY FLOWCHART



RANDOMISATION AND BLINDING

Study participants will be randomised to either a CCT group or a control group on a 1:1 ratio via sequence generation using a random number generator. An independent investigator will generate allocation sequence codes using a computer generated list of randomised numbers which will be stored digitally using and encrypted password at the UoL. The allocation sequence codes will be concealed from the chief investigator, statisticians, trial members and all participants involved in this study. The chief investigator will be responsible for enrolling and assessing participants. Randomisation will take place after the enrolment/screening visit. To enter a participant into the study, the chief investigator will ask the independent investigator to read the next treatment code and tell them what group the participant is to be randomised to.

STUDY REGIMEN

Cognitive training group

Study enrolment visit

The purpose of this visit is to 1) have any questions potential participants may have answered, 2) receive informed consent from eligible participants, 3) screen participants for any cognitive impairments using the MMSE, and 4) have participants complete the study enrolment form. Screening and enrolment visits will take place either in the SSB, UoL, or in the participant's home. In the event that a participant's MMSE score is identified as 23 or below, participants will be reassured that cognitive decline is a natural process associated with ageing and that the tests scores are only indicative and provide no clinical diagnosis. If concerned, participants will be advised to seek further information from their GP.

Baseline assessment visit

The purpose of this baseline assessment visit is to 1) extract venous and capillary blood samples and 2) obtain baseline cognitive function scores. Initially, venous and capillary blood samples will be extracted for the purpose of BDNF and HbA1c measurements. Venous blood samples will be frozen, and batch analysed using ELISA technique to identify levels of BDNF. Following blood extraction, participants will then be required to conduct a computerised neurological test battery that will assess their cognitive function (Appendix A). This test battery will take approximately 35 – 45 minutes to complete. The baseline assessment will take place in a psychology laboratory located in the SSB, UoL. Venous blood extraction will take place in a psychology laboratory, SSB, UoL and will be frozen, stored and analysed in a wet laboratory, SSB, UoL.

Intervention visits

Individuals randomised to the cognitive intervention arm will participate in a CCT programme. Participants will be required to complete a total of 12 hours of cognitive training over a 4-6 week period, with sessions being performed 2-3 per week. Each cognitive session will require the participant to perform a series of computerised cognitive tasks (Appendix B). Each cognitive task will be conducted using a specialist touch screen laptop utilising software developed by Cambridge cognition lasting approximately 60 minutes in duration. Intervention visits will take pace either in the CANTAB laboratory, SSB, UoL, or in the participant's home.

Post-intervention assessment visit

The purpose of this post intervention assessment visit is to 1) extract venous blood samples to assess post-intervention BDNF levels, 2), obtain post intervention cognitive function scores and 3) gain qualitative feedback using evaluation questionnaires. Post-intervention assessment visit will take place in the CANTAB laboratory, SSB, UoL.

Control arm

Individuals allocated to the control group will attend screening/enrolment, pre-intervention and post-intervention assessments only. Controls will receive usual care.

SCHEDULE OF PROCEDURES

Procedures	Screening/ enrolment	Baseline assessment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Post-intervention assessment
PIS	X								
ICF	X								
MMSE	X								
Education status	X								
Computerised test battery		X							X
BDNF samples		X							X
HbA1c		X							
Cognitive training			X	X	X	X	X	X	
Interviews									X
Evaluation Questionnaire									X

WITHDRAWAL

Participants may be withdrawn from the trial either at their own request or at the discretion of the CI. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the PIS and ICF) that should they withdraw the data collected to date cannot be erased once data analysis has begun and may still be used in the final analysis.

ETHICAL AND REGULATORY CONSIDERATIONS

ASSESSMENT AND MANAGEMENT OF RISK

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

ETHICS REVIEW AND COMPLIANCE

The study shall not commence until the study protocol, information sheets and consent forms have been reviewed and approved from a research ethics committee and relevant NHS/social care permission is obtained.

The sponsor will be responsible for deciding whether amendments are substantial and non-substantial in collaboration with the CI.

Where an amendment is required to study documentation that required REC approval, changes will not be implemented until REC approval and Health Research Authority (HRA) categorisation is received. Where an amendment requires local approval, this shall be sought prior to the amendment being implemented at each site in accordance with the categorisation given on the HRA approval letter.

Should an amendment be required to eliminate an apparent immediate hazard to participants this may be implemented immediately, and the REC/HRA and research and development (R&D) will be notified as soon as possible.

Minor amendments for logistical or administrative purposes may be implemented immediately.

Amendments will be logged on the sponsor's study amendment log and stored in the trial master/site file(s).

Annual progress reports shall be submitted to the research ethics committee within 30 days of the anniversary date on which the favourable opinion was given – until the end of the study. A final report shall (where possible) be submitted to the research ethics committee within one year after the end of the study.

If the study is terminated prematurely the CI will notify the REC, including the reasons for premature termination.

PEER REVIEW

The protocol for this studies was reviewed by the co-investigators/protocol contributors on several occasions over the course of protocol development.

PUBLIC & PATIENT INVOLVEMENT

An overview of the project plan has been presented to a group of patients at a Diabetes UK support group who were given the opportunity to comment on the research question and protocol. All patients were very interested and knew little about cognitive function and its accelerated decline in T2DM.

PROTOCOL COMPLIANCE

Accidental protocol deviations may occur at any time. Accidental protocol deviations will be adequately documented on the relevant forms and reported to the CI and sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, these will require immediate action and could potentially be classified as a serious breach.

DATA PROTECTION AND PATIENT CONFIDENTIALITY

All study staff and investigators will comply with the principles of the Data Protection Act 1998 (replaced by the General Data Protection Regulation May 2018) in protecting the rights of study participants with regards to the collection, storage, processing and disclosure of personal information and will uphold the act's/regulations core principles.

Each participant will be assigned a study identity number, for use on trial documents and the electronic database.

Personal data, research data and the linking code will be stored in separate locations. When stored electronically, this will include using encrypted digital files within password protected folders and storage media. Personal information shall be stored separately to research data and will be kept secure, and maintained.

All research and personal data, including extracted blood samples, will be kept securely for a minimum of 5 years in accordance with university policy. Extracted blood samples will be securely stored in the SSB, UoL and will be available for future use. Extracted blood samples will be 'not relevant material' for purpose of HTA.

Data generated as a result of this study will be available for inspection on request by the participating physicians, UoL representatives, the REC, local research and development departments and the regulatory authorities.

INDEMNITY

The University of Lincoln as research sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance.

ACCESS TO THE FINAL DATASET

The CI will have access to the final dataset only.

DISSEMINATION POLICY

The data custodian will be the CI on behalf of the UoL.

Strategies for the dissemination of research will include submission to a peer-reviewed scientific journal in an appropriate field of research, presenting findings at research conferences and local diabetic communities in the form of abstracts and posters form, and through a doctoral thesis.

Authorship eligibility guidelines and any intended use of professional writers

All authors for this trial will meet the four following criteria for authorship in line with The International Committee of Medical Journal Editors:

Provide substantial contribution to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work

Contributing to draft copies of work and revising it critically for important intellectual content

Review and approve the final version for publication

Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Appendix O - Participant information sheet

Participant Information Sheet
(Final version 1.1 Date 31/05/18)

Title of study: Investigating the effect of a brain training intervention on brain function in type 2 diabetes

IRAS ID: 227672

Name of Researcher(s): Samuel Cooke, Dr. Ffion Curtis, and Dr. Kyla Pennington

You are being invited to take part in a research study. Before you decide if you want to take part it is important to explain why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

1. What is the purpose of this research?

This research study is being undertaken as part of a PhD thesis to help better understand how brain training may help improve brain health in people with type 2 diabetes. Having diabetes may increase the risk of developing dementia and Alzheimer's disease. It is important to find ways to help people with diabetes have healthier brains for longer. We know that brain training can help improve brain health in people without diabetes, but we don't know if this is the same for people with type 2 diabetes.. We are doing this research to gather evidence on the effect brain training has on brain function in people with type 2 diabetes to help design a future larger study.

2. Why have I been chosen?

We are asking you to take part in this study because you are 45 years of age or older and have type 2 diabetes.

3. Do I have to take part?

It's up to you to decide whether or not to take part. Please read and keep this information sheet to help you decide whether you wish to take part. If you decide to take part you will be asked to sign a consent form. You are free to stop and withdraw from the study at any time, without giving a reason. This will not affect your usual health care in any way, or your medical or legal rights and we will respect your decision.

4. What happens if I decide not to take part in the study?

If you decide not to take part in this study then you will carry on with your usual diabetes care.

5. What will happen to me if I take part?

Initially you will be invited to take part in a study enrolment visit. The purpose of this visit is to 1) invite you to provide consent, 2) complete a brief cognitive screening test, and 3) complete a study enrolment form. This visit can be completed either at the University of Lincoln or in your own home and will take approximately 30 minutes. You will then be invited to the University to complete the pre-study measurements. This visit will require you to 1) Give a small blood sample for the analysis of HbA1c and BDNF (a marker of brain function), and 2) undergo a series of computerised brain tests to assess your brain function. This visit will take approximately 1 hour.

Following this, you will be assigned into either a brain training group or a comparison group. This will be done through a process called randomisation. Randomisation uses chance to divide people in to groups, just like flipping a coin (e.g. people who flip a head go into one group and people who flip a tail go into another group).

If you are randomised into the brain training group, you will be invited to complete 12 hours of computerised brain training over a 4-6-week period. Brain training sessions will last no more than 1 hour and you can chose to do this two or three times a week. You will have the option of completing these sessions either at the University of Lincoln or in your own home under the supervision of the researcher. If placed into the comparison group, you will carry on with life as usual for the 6 weeks.

You will then be invited back to University of Lincoln to complete the post-study measurements (the same as the pre-study measurements) and complete a study evaluation questionnaire. Finally, you will then be invited to take part in an optional telephone interview, where you will answer questions and discuss your experience of the study. All telephone interviews will be audio-recorded by Samuel Cooke who will also be responsible for transcribing the recordings word for word. Transcription will take place any time after the telephone interview.

The time commitment will differ depending on what group you are randomly assigned to. The time commitment for the brain training group will be approximately 15 hours over a 6-8 week period. The time commitment for the usual care group will

be approximately be 3 hours over a 6-8 week period. There will be no continued provision of the intervention at the end of the study.

6. Expenses and payments

You will not be paid (an inconvenience allowance) to participate in the study. Travel expenses will be offered to those travelling to and from the University of Lincoln. You can claim for travel expenses by completing a Non Staff Expenses form and returning it to a member of the research team. A paper version of the form can be downloaded from the Uiversity's website or if you don't have access to the internet or printing facilities then the researcher can send a form to your address. The form can be sent back using freepost. Reimbursement of travel expenses will include petrol fare (45p per mile up to 100 miles on return journeys), bus fare, train fare and parking.

7. What are the possible risks of taking part?

The main risk associated with this study is giving blood and prolonged computer use during brain training. The risks involved in drawing blood from a vein may include, momentary discomfort at the site of the blood draw, possible bruising and bleeding at the site, feeling of light-headedness when the blood is drawn, and rarely, an infection at the site of the blood draw. Every effort will be made to make you feel comfortable when giving blood. Through the researcher following the correct training techniques and abiding to the health and safety protocols, the risk of bleeding, bruising, and infection will be minimised. The risks involved with prolonged computer use may include, fatigue, prolonged poor seated posture, repetitive movements, and eye strain. To counteract such problems the researcher will ensure that you will be given regular breaks and are comfortable when conducting the brain training.

8. What are the benefits of taking part?

You will be part of new and exciting research that could help people with diabetes keep healthier brain function for longer. If placed into the brain training group, you will get individual feedback from the different brain training tasks.

9. What happens if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting either the University of Lincoln, School of Psychology Ethics Committee (SOPREC), contact email: soprec@lincon.ac.uk Telephone: 01522 886190, or by contacting the Patient Advice and Liaison Service (PALS), contact email: LHNT.LincsPAL@nhs.net Telephone: 0300 123 9553.

If you score 23 or below on the cognitive screening test, indicating cognitive impairment, then unfortunately you will not be able to take part in this study. A decline in brain function is a natural process associated with aging, and although a score of 23 or below is indicative of mild cognitive impairment, this test is not a clinical diagnosis and is only a suggestive outcome. If you are concerned we recommend you seek further information from your GP.

10. Will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence. If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Lincoln who are organising this research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty. All information which is collected about you during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the university will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

All research and personal data will be kept securely for a minimum of 5 years in accordance with university policy. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data. Information will not be made available to any life insurance or private medical insurance companies, but our regulatory bodies may request to view the anonymised data.

11. What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw once analysis has begun, then the information collected so far cannot be erased and this information may still be used in the project analysis. Any remaining samples will be destroyed as required.

12. What will happen to any samples I give?

As part of this study we will take venous and capillary blood samples from you to help us determine your brain function and blood sugar levels. Venous blood samples will be taken from a vein situated in the pit of your elbow on either your right or left

arm. Venous blood samples will be used to determine levels of a protein called brain-derived neurotrophic factor, a marker of brain health. Capillary blood samples will be taken from your right index finger using a finger prick test. Capillary blood samples will be used to determine levels of glycated haemoglobin, in other words your blood sugar levels.

We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to you and securely at the University of Lincoln under the University's Human Tissue Research Licence (no XXXXX). Some of these future studies may be carried out by researchers other than current team, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

13. What will happen to the results of this study?

If you do take part in this study only the research team will have access to information collected during the study. If you take part you will be agreeing that we can use data collected from you for the purpose of research. The results may be published in scientific journals, presented at conferences and included in a doctoral thesis, however, all data will be anonymised (individual names will not be used). You will be given the option to receive a summary of your results.

14. Who is organising and funding the research?

This research is being organised and funded by the University of Lincoln.

15. Who has reviewed this study

All research conducted by the University of Lincoln is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the University of Lincoln Research Ethics Committee and the Health Research Authority/Leicester Central Research Ethics Committee.

16. Insurance arrangements

The University of Lincoln as research sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials.

17. I would like to take part, what should I do now?

Please complete the expression of interest form attached and return it in the pre-paid envelope provided. A member of the research team will then contact you by telephone.

18. Who is responsible for the study and who should I contact?

Samuel will be your main study contact and will explain all the project details so that you feel comfortable with knowing exactly what will be what be required. We are very grateful should you choose to take part in this research project, we will treat you with respect at all times and try our best to explain everything to you so that you have a positive experience. If you have any questions regarding the study please feel free to contact Samuel at any time.

Samuel Cooke

Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS

Email: scooke@lincoln.ac.uk

Other members of the research team

Dr. Ffion Curtis Email: fcurtis@lincoln.ac.uk

Dr. Kyla Pennington Email: kpennington@lincol.ac.uk

Appendix P – Informed consent sheet

IRAS Project ID: 227672
Participant Identification Number for this study:

CONSENT FORM

Title of Project: Investigating the effect of a computerised cognitive training intervention on cognitive function in type 2 diabetes mellitus.

Name of Researcher: Samuel Cooke

Please initial box

1. I confirm that I have read the information sheet dated 31st May 2018 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I understand that should I withdraw, the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Lincoln, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records, I understand that my personal details will be kept confidential. ☐
4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. **OPTIONAL** ☐
5. I understand and agree that a blood sample will be taken for analysis of biomarkers of brain function and blood sugar levels. ☐
6. Consent for storage and use in possible future research **OPTIONAL** ☐
   I agree the samples I have given and this information gathered about me can be stored by the University of Lincoln at the Sarah Swift Building, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study including researchers working for commercial companies. Any future studies will be subject to ethical review. Any samples or data used will be anonymised, and I will not be identified in anyway.
7. I would like to receive a summary of the results of the study ☐

8. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix Q – Study recruitment poster

UNIVERSITY OF LINCOLN
LINCOLN INSTITUTE FOR HEALTH

Do you have Type 2 Diabetes?

Would you be interested in Brain Training?

If so.....

We are currently recruiting people who are aged **45 years +** and diagnosed with **type 2 diabetes** to take part in an exciting brain training study.
The aim of the study is to investigate the effect of a brain training program on brain function in type 2 diabetes.

What does this study involve?
12 brain training sessions over 4-6 weeks (you can complete these at home or at the University of Lincoln). You will also come to the University before and after the brain training to take important study measurements.

What are the benefits?
You will be part of new and exciting research that could help people with diabetes keep healthier brain function for longer! You will also get individual feedback from the different brain training tasks.

Any questions, interested? Please contact Mr. Samuel Cooke
Email: scooke@lincoln.ac.uk

Appendix R - Expression of interest form

Expression of Interest Form

(Final version 1.0 Date 05/04/18)

I give permission for the principal researcher (Samuel Cooke) to contact me regarding participation in this study.

Name……..

Signature……

Date ……..

Contact details

Address

……

……

……

Contact telephone ……..

Contact email……

Preferred method of contact: Email ☐ Telephone ☐

Preferred time of contact: Morning ☐ Afternoon ☐ Evening ☐

Comments

*** Please return to the researcher using pre-paid envelope ***

Appendix S – Study debrief form

Study Debrief form

"Investigating the effect of a brain training intervention on brain function in type 2 diabetes mellitus"

The researchers would like to thank you for your participation in this research project. This study aimed to test the effect of a brain training programme on brain function in type 2 diabetes mellitus. It has been shown that brain training is effective in improving brain function in healthy individuals. However, the evidence in type 2 diabetes mellitus is limited. Therefore, it is important for us to further explore the effect of a cognitive intervention as it is still unclear as to what kind of effect it will have in a type 2 diabetes population.

How was this tested?

In this study, you were invited to complete 12 hours of brain training over a 4-6 week period. At the start of the study you completed a pre-study visit in which we measured your brain function and took blood samples to measure BDNF and blood sugar levels before taking part in either the brain training or usual care group. You also attended a post-study visit in which we measured your brain function, BDNF and blood sugar levels after you completed the brain training or usual care group. To test the effectiveness of the brain training intervention on brain function in type 2 diabetes mellitus, we compared the pre and post scores of those individuals who completed the brain training intervention against the scores of those individuals who completed usual care.

Hypotheses and main questions:

We are interested in knowing what effect brain training has on brain function and BDNF levels in type 2 diabetes individuals. We hypothsised that 12 hours of brain training would improve brain function and BDNF levels in individuals with type 2 diabetes mellitus.

Why is this important to study?

The number of people with type 2 diabetes mellitus in the UK is increasing as are the associated complications such as heart disease, stroke, nerve damage, eye damage, kidney disease, and brain impairment. Ultimately, diabetes-induced brain impairment considerably increases one's risk of developing severe brain complications such dementia and Alzheimer's disease imposing a significant burden for both the individual and their care provider. Brian impairment, however, has not been targeted by current UK management strategies set out for type 2 diabetes mellitus. The current study is important as it may contribute to the development of novel interventions and thus management/treatment strategies for preventing/improving brain impairment within type 2 diabetes mellitus.

What if I want to know more?

If you are interested in learning more about type 2 diabetes mellitus and brain function and how brain training may influence this relationship, please see below for further information.

1) https://www.diabetes.org.uk/Documents/Position%20statements/DiabetesUK_Facts_Stats_Oct16.pdf

2) Kodl, C.T. & Seaquist, E.R. (2008) Cognitive Dysfunction and Diabetes Mellitus. Endocrine Reviews, 4(29) 494-511.

3) Mowszowski, L., Lampit, A., Walton, C.C. & Naismith, S.L. (2016) Strategy-Based Cognitive Training for Improving Executive Functions in Older Adults: a Systematic Review. *Neuropsychological Review,* 3(26) 252-270.

Thank you again for your participation in this study, if you have any further questions or queries regarding this study please find contact details below.

Mr. Samuel Cooke
Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS Email:

Dr. Ffion Curtis
Lincoln Institute for Health, University of Lincoln, Brayford pool, Lincoln, LN6 7TS Email: fcurtis@lincoln.ac.uk

Dr. Kyla Pennington
School of Psychology, University of Lincoln, Brayford pool, Lincoln, LN6 7TS
Email: kpennington@lincol.ac.uk

Appendix T – CONSORT checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	93
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	N/A
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	93,94
	2b	Specific objectives or research questions for pilot trial	95
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	95
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	Recommendations for changes described in Chapter 2
Participants	4a	Eligibility criteria for participants	96
	4b	Settings and locations where the data were collected	95
	4c	How participants were identified and consented	96 (Recruitment), 97 (Enrolment visit)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	98 (Intervention) 99 (Control)
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	99, 100 (Feasibility), 100 (Cognition and BDNF)
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	Recommendations for changes described in Chapter 2
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	100, 101

Sample size	7a	Rationale for numbers in the pilot trial	95
	7b	When applicable, explanation of any interim analyses and stopping guidelines	95
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	95
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	95
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	95
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	95
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	101-102
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	103
	13b	For each group, losses and exclusions after randomisation, together with reasons	103
Recruitment	14a	Dates defining the periods of recruitment and follow-up	95
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	104
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	102 (Feasibility and Cognition), 118 (BDNF)
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	104–111 (Feasibility) 112-115 (Cognitive) 118-120 (BDNF)
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	113 (Cognition correlations), 115-117 (Training performance Appendix W), 118-120 (BDNF correlation and scatter plot)
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for	N/A

		harms)	
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	128-129
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	122-127
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	122-127
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	122 – 124
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	N/A
Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	N/A
	26	Ethical approval or approval by research review committee, confirmed with reference number	95

Appendix U – Human tissue research procedure

Human Tissue - Research Procedure

For Venous/capillary blood sample extraction

Version 1.0 Date 05 July 2018

UNIVERSITY OF LINCOLN

Scope

Applicable to all staff and students who are performing venepuncture for the collection of venous and capillary blood from research participants. It should be noted, this procedure does not cover the administration of any drug (or other substances) intravenously, intramuscularly, or sub-cutaneously. The nature of the work associated with venous and capillary blood extraction presents unique health and safety issues by following this work instruction staff and students will be made aware of all potential risks and hazards and are adequately minimised. For the purposes of clarification staff and students undertaking phlebotomy will be referred throughout this document as researchers.

Training

It is the responsibility of the study Principal Investigator to ensure that all researchers involved in collecting samples have been adequately trained in the procedures used to collect, handle, transport and store samples including the University's Human Tissue Quality Management System (HT-QMS).

Researchers who will take blood must have completed formal training in phlebotomy. This may have been during broader clinical training (e.g. doctors, nurses, trained phlebotomists) or, for non-clinical staff, the phlebotomy training course provided by various NHS Trusts or external agencies. As some of these courses involve training on mannequins, staff who complete them must only take blood from participants under direct clinical supervision until a fully trained clinician (i.e. doctor, nurse, phlebotomist) is satisfied that they may perform the procedure safely on their own.

As participants may sometimes faint before, during or after the taking of blood, at least one member of staff (present in the building) must be trained in basic life support. Lastly all staff performing phlebotomy must have evidence of Hepatitis B immunity following immunisation and be fully up to date with the standard vaccination schedule, including tetanus.

Phlebotomy must only be performed by a trained staff or student (or under supervision for those still training).

Appropriate Facilities

Appropriate facilities must contain the required levels of equipment, and services to safely perform phlebotomy. Specifically this includes:

Equipment

Tourniquet, latex gloves, vacutainers, capillary tube, sterile needles including butterfly needles, sterile safety lancet, cotton wool, alcohol wipes/sterile swab, plasters, clean equipment trays and medical tape.

The facility must have an appropriately private room with clean, wipe able surfaces, in which phlebotomy can be performed and which contains a comfortable chair or bed for participants with a cushion/pillow/arm brace to support participants' arms while blood is being drawn.

Basic facilities for dealing with participants who faint (or feel faint) during phlebotomy should be provided—somewhere they can lie down (with their legs raised if necessary).

Services

An appropriate sharps disposal service must be in place (i.e. there should be sharps disposal bins which are regularly checked and safely disposed of). The facility must have a needle stick policy in place, which includes a clear statement about who to contact in the event of a needle stick injury.

There must also be an appropriate laboratory for processing the blood samples, or an established safe system for transporting the samples to such a laboratory.

Information Provided to Research Participants

A Participant Information Sheet should be provided which clearly outlines all procedures involved in the research study.

Where appropriate a PIS should also include a statement that, before the sample is taken, consent will be sought to enable the researchers to forward the results to the participant's GP in the case of a clinically significant abnormal result for further investigation (researchers may also consider restricting recruitment of participants to those already registered with a GP). It should be noted that samples collected for a research study may need to be repeated for diagnostic purposes. As well as a statement that the participant will be informed in advance if any findings are to be forwarded.

PIS should follow the University template: Info sheet template (including human tissue).

Consent of Research Participants

Informed consent should be recorded on a consent form which includes explicit consent for the taking, storing and testing of the samples.

Where appropriate the consent form should also contain a clause in which consent is obtained for contacting their GP in the event of a clinically significant abnormal result as well as a

clause that the participant understands that they will be informed in advance if findings are to be forwarded.

Consent forms should follow the University template: Template Consent Form – Human Tissue.

Financial and Other Rewards to Participants

An inconvenience allowance may be offered to participants – this must be approved by an ethics committee (University or HRA).

Potential Risks Associated with Venous and Capillary Blood extraction

Risks to the participants

Common risks associated with phlebotomy are pain during the procedure and bruising (with associated pain afterwards). These risks will be minimised by ensuring that all staff are fully trained in phlebotomy. Bruising after the event will also be reduced by promptly applying pressure on the puncture site after the needle is withdrawn. All participants will be fully informed about these risks in the Participant Information Sheet. The worry associated with taking blood may cause some participants to feel unwell or faint before, during or after the procedure. The risk associated with this will be reduced by having an adequately equipped facility for performing the procedure and having a staff member trained in basic life support.

Although phlebotomy is a very safe procedure, it does create a puncture wound on the skin which may very rarely lead to infection around the puncture site. The risk of this will be minimised by ensuring strict hygiene during the procedure and by not recruiting participants who are at increased risk of infection. In the event that a participant reports symptoms of an infection (local redness, swelling, pain or discharge of pus) they should be referred to their GP or to A&E urgently.

Risks to the researcher

Taking blood carries a risk of needle stick injury to the phlebotomist, which in turn carries a risk of exposure to blood borne infections. This risk will be minimised by a) ensuring staff are adequately trained in phlebotomy, and b) ensuring staff have been vaccinated against, and show immunity to Hepatitis B. The risk of exposure to infection is increased in all those involved in the collection, transport, storage or processing of any biological material. This risk will be minimised by ensuring all staff involved in these procedures are adequately trained and that the appropriate equipment and facilities for the safe handling of samples is provided.

Monitoring and Reporting of Adverse or Unforeseen Advents
Adverse or unforeseen events will be reported to the departmental safety officer in the first instance and may be followed up by the University Safety officer if deemed necessary. The Human Tissue Oversight Group should also be notified of such events.

Duty of Care Issues/Confidentiality

Duty of care and confidentiality issues arise largely due to the results of tests on the samples, rather than taking of the samples per se. This procedure does not cover issues concerned with the testing of the samples, although it is expected that studies will have in place a system by which the results of the tests performed are reviewed and, where necessary, further investigations or referrals are made. The confidentiality of the results are also expected to be maintained in accordance with University policy.

Data Protection

Research data including consent forms should be stored in accordance with University policy.

Where samples are stored under the University's Human Tissue Licence a copy of the consent form must be held by the University's Designated Individual in accordance with the HT-QMS specifically SOP HT05 Storage. Consent forms may be held under legal basis (GDPR).

Storage

Joseph Banks Laboratories (JBL): Samples should be held in accordance with SOP HT05 Storage.

Sarah Swift Building (SSB): Samples should be held in accordance with SOP HT05 Storage.

Samples must be rendered acellular within 7 days, otherwise if samples are to be kept beyond 7 days samples and are relevant material, they must be transferred to Joseph Banks Laboratories (JBL) and held under the universities Human Tissue Licence. Otherwise samples should be destroyed

Where HRA REC approval has been obtained then samples may be stored for the duration of the study. Once the study is complete samples should be transferred or disposed of in accordance with the ethics application and favourable opinion.

Venepuncture Criteria

The procedure for venous and capillary blood extraction is intended for use when the following criteria are met:

- The study involves participants who are able to provide informed consent.
- Where venous blood samples will be taken, a maximum of 50ml of venous blood will be taken from either the anti-cubital fossa, lower arm or back of the hand by a researcher trained in phlebotomy (see section 2).
- Where blood is taken, this should be carried out in an appropriate facility (see section 3).
- Researchers involved in the collection, handling, transport or storage of samples have received appropriate training (see section 2).

Blood Extraction Procedures

Venous blood extraction

- Any cuts on the researcher's hands or wrists should be covered with a waterproof adhesive dressing prior to taking samples.
- Prepare the work area/tray with the necessary equipment – this should include:
    - Vacutainers
    - Tube safety holders
    - Sterile needles
    - Tourniquet
    - Tube rack
    - Alcohol wipes/sterile swabs
    - Sample tubes/test strips
    - Hazardous waste bin
    - Sharps container
    - Tissue/ cotton wool pads
- Wash hands thoroughly prior to sampling.
- Disposable latex gloves must be worn when taking and handling samples. New gloves must be worn for each participant.
- Apply tourniquet to the upper middle part of the chosen arm and palpate potential site of puncture to identify the most optimal location for venous blood collection.
- Swab the chosen puncture site (Either anti-cubital fossa, lower arm, or back of the hand) with a sterile swab and dispose of the swab in the hazardous waste bin.
- Puncture the cleaned area using a sterile needle and fill the vacutainer with approximately 6ml of venous blood. Depending on how many samples are being collected, remember to remove tourniquet on the last collect to aid flow.
- Once the sample has been collected, gently remove the needle from the puncture site remembering to apply a cotton wool pad to stem any bleeding. Place collected blood samples in a tube rack holder and label where appropriate
- Used needles must be placed in the sharps container immediately after use. The sharps container must be closed when the experiment is finished. All swabs, gloves and non-sharp material should be placed in a yellow hazardous waste bin.
- Any spilled blood should be cleaned with appropriate disinfectant and discarded into hazardous waste.
- Wash hands before leaving the laboratory.

Capillary blood extraction

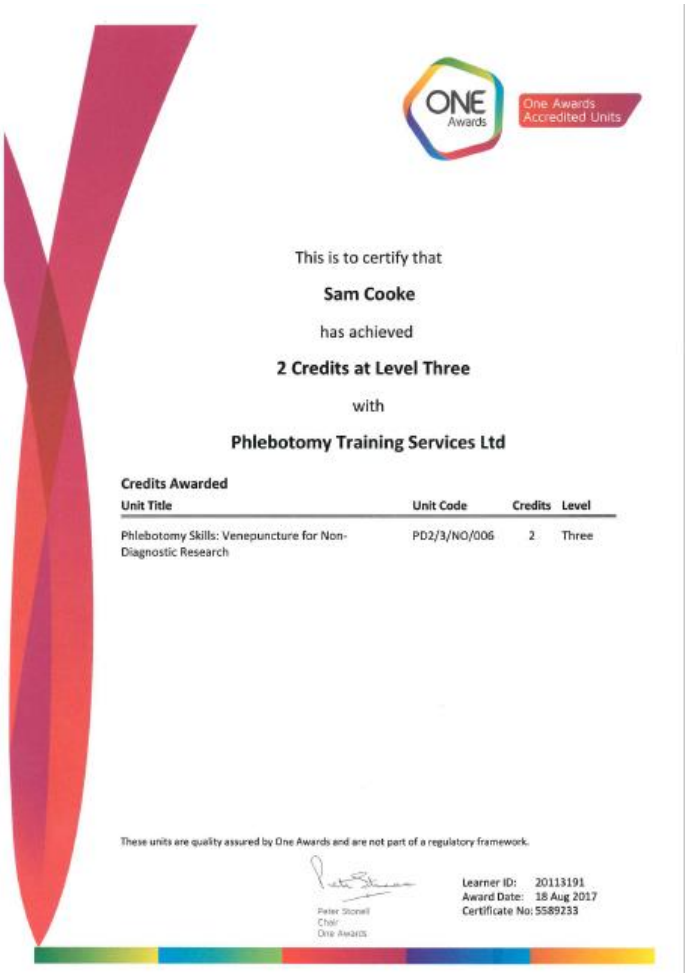
- Any cuts on the researcher's hands or wrists should be covered with a waterproof adhesive dressing prior to taking samples.
- Prepare the work area/tray with the necessary equipment – this will include:

    - Lancet device
    - Alcohol wipes/Sterile swabs
    - Sample tubes/test strips
    - Tube rack
    - Hazardous waste bin
    - Sharps container
    - Tissue/ cotton wool pads
- Wash hands thoroughly prior to sampling.
- Disposable latex gloves must be worn when taking and handling samples. New gloves must be worn for each participant.
- Employ a 'no touch' technique as far as possible.
- Swab the site of the puncture (ear lobe or fingertip) with a sterile swab and dispose of the swab in the hazardous waste bin.
- Puncture the cleaned area using the lancet device and gently massage the sample site to form a large droplet of blood.
- Using a tissue/cotton wool pad wipe away the first droplet, then repeat the technique to form a second droplet of blood.
- Place the capillary tube to the blood and the blood should enter the tube via capillary action, repeat until the capillary tube is one-third to one-half full.
- Wipe the sample site clean with a tissue/ cotton wool pad.
- Used lancets must be placed in the sharps container immediately after use. The sharps container must be closed when the experiment is finished. All swabs, gloves and non-sharp material should be placed in a yellow hazardous waste bin.
- Any spilled blood should be cleaned with appropriate disinfectant and discarded into hazardous waste.
- Wash hands before leaving the laboratory.

Further Information

For further information on drawing blood see WHO guidelines on drawing blood: best practices in phlebotomy
http://apps.who.int/iris/bitstream/handle/10665/44294/9789241599221_eng.pdf;jsessionid=AF310C8B5DE6C0CA8B1E15015E6860C2?sequence=1

Appendix V – Phlebotomy training certificate



ONE Awards

One Awards Accredited Units

This is to certify that

Sam Cooke

has achieved

2 Credits at Level Three

with

Phlebotomy Training Services Ltd

Credits Awarded

Unit Title	Unit Code	Credits	Level
Phlebotomy Skills: Venepuncture for Non-Diagnostic Research	PD2/3/NO/006	2	Three

These units are quality assured by One Awards and are not part of a regulatory framework.

Peter Stonell
Chair
One Awards

Learner ID: 20113191
Award Date: 18 Aug 2017
Certificate No: 5589233

Appendix W - Training performance

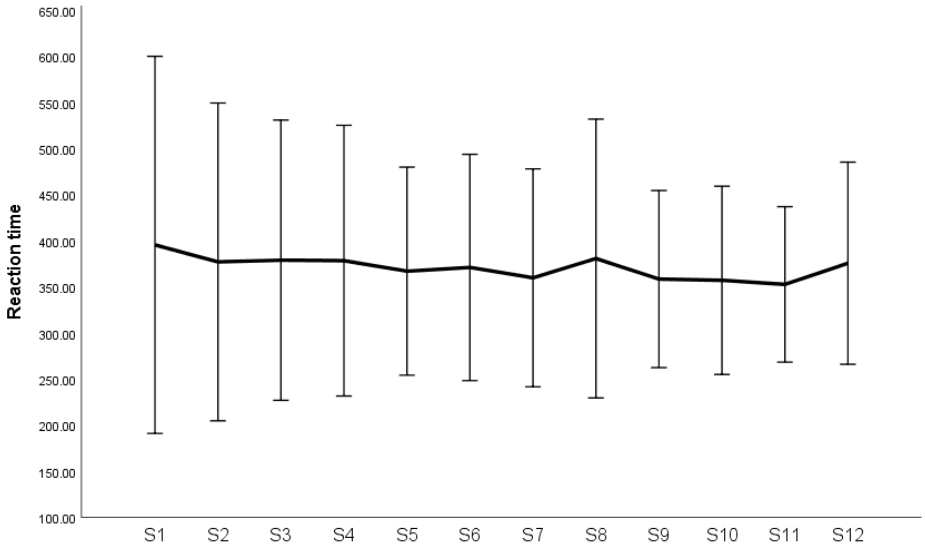


Figure 1. Choice Reaction Time (CRT) – Median reaction time

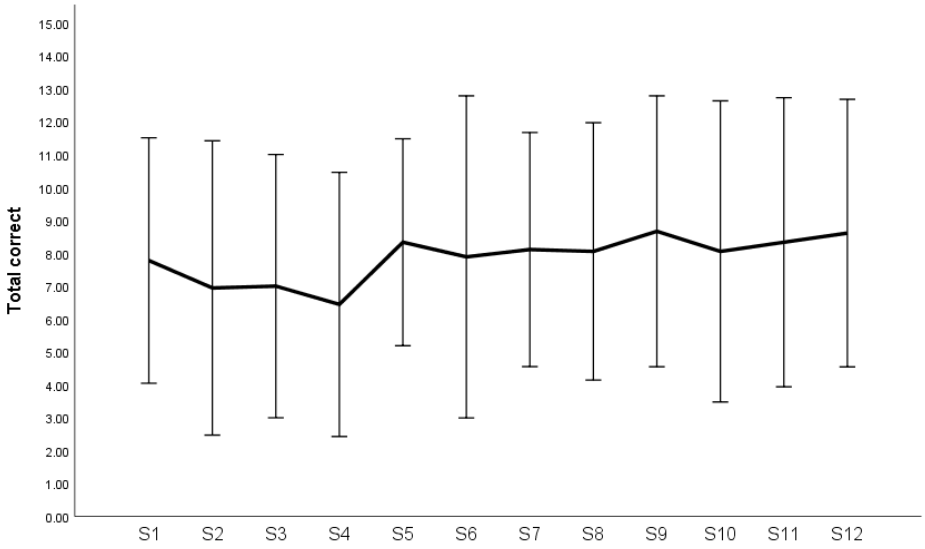


Figure 2. Verbal recognition Memory (VRM) – Free recall total correct

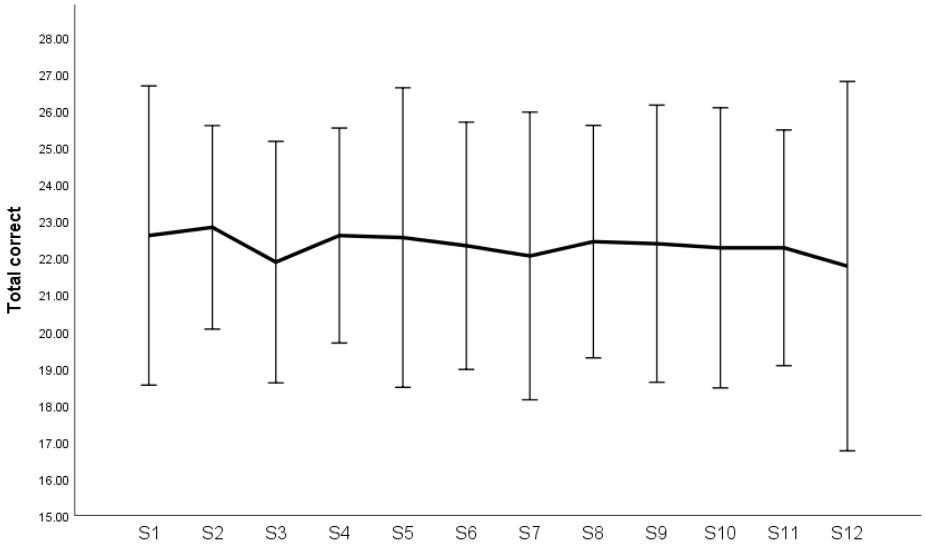


Figure 3. Verbal recognition Memory (VRM) – Recognition total correct

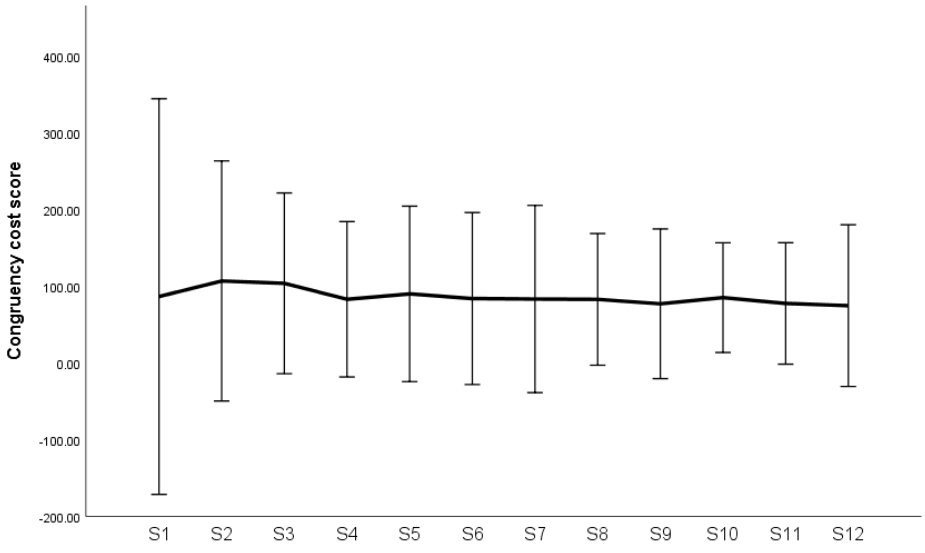


Figure 4. Attention Switching task (AST) – Congruency cost

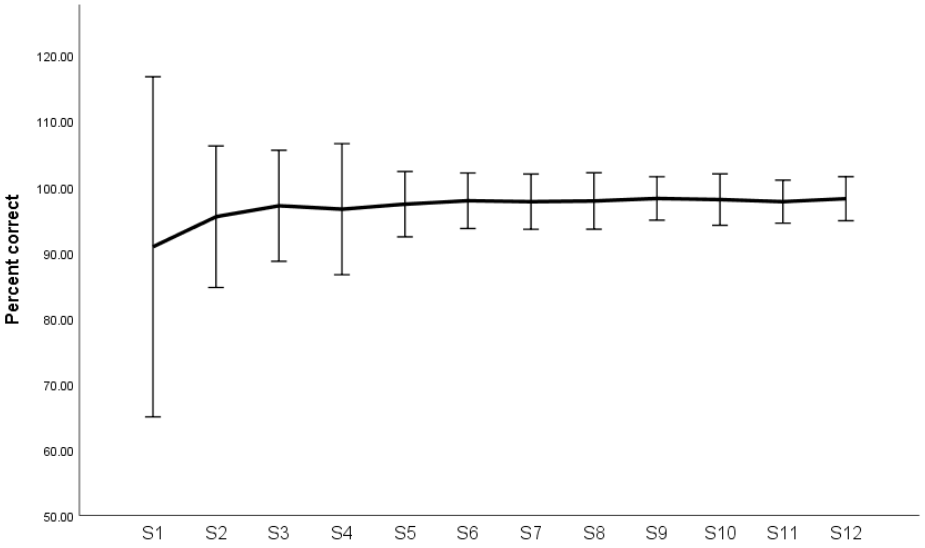


Figure 5. Attention Switching Task (AST) – Percent correct

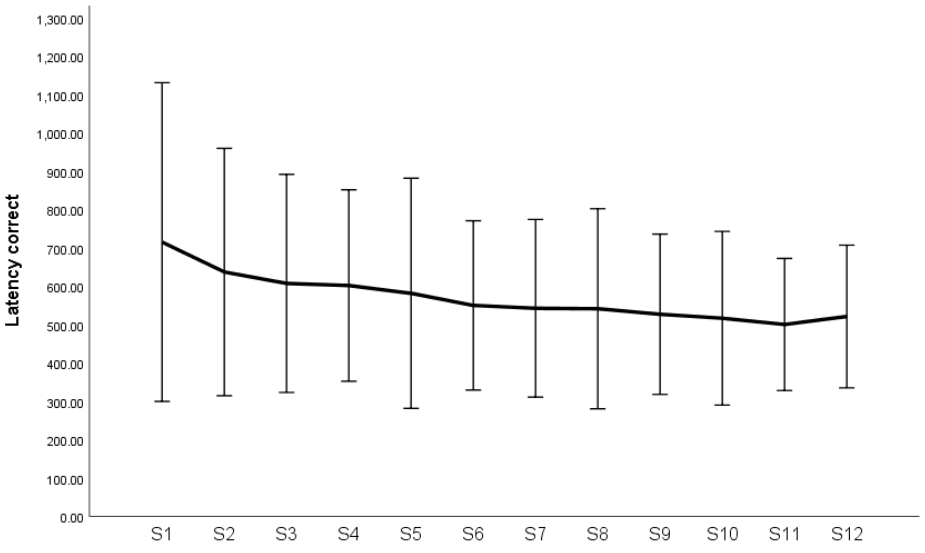


Figure 6. Attention Switching Task (AST) – Median latency

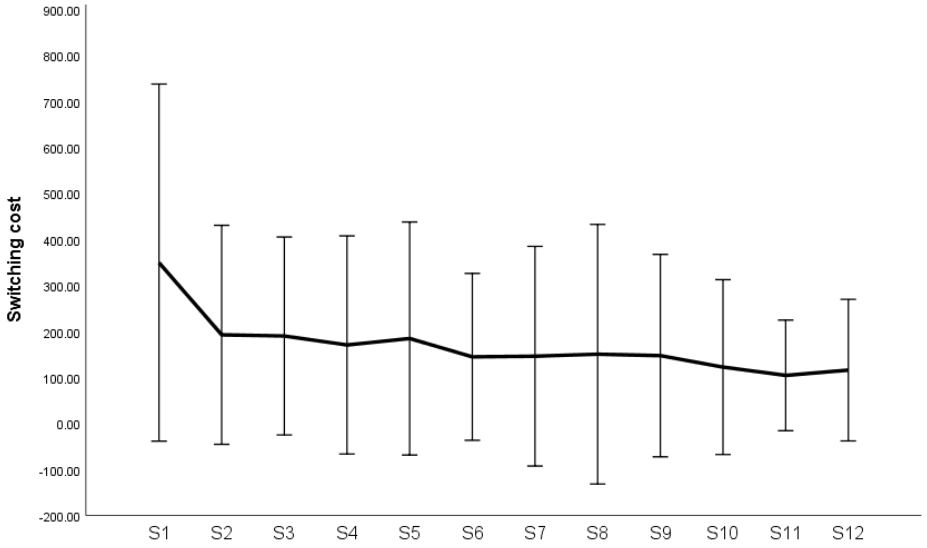


Figure 7. Attention Switching Task (AST) – Switch cost

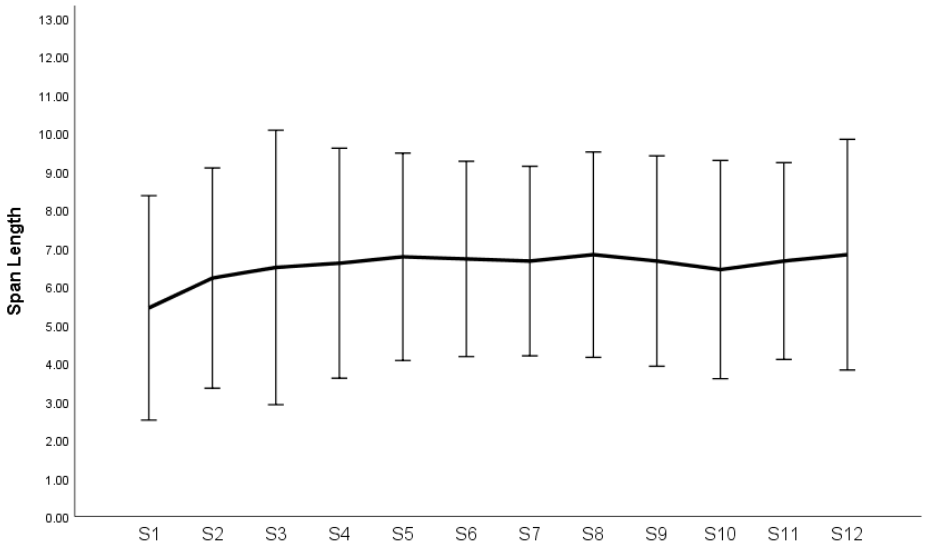


Figure 8. Spatial Span (SSP) – Span Length

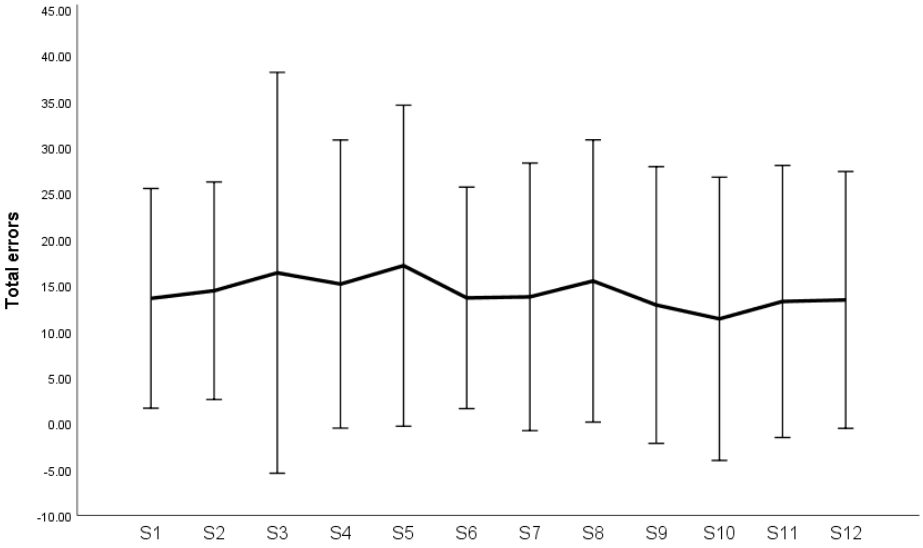


Figure 9. Spatial Span (SSP) – Total Errors

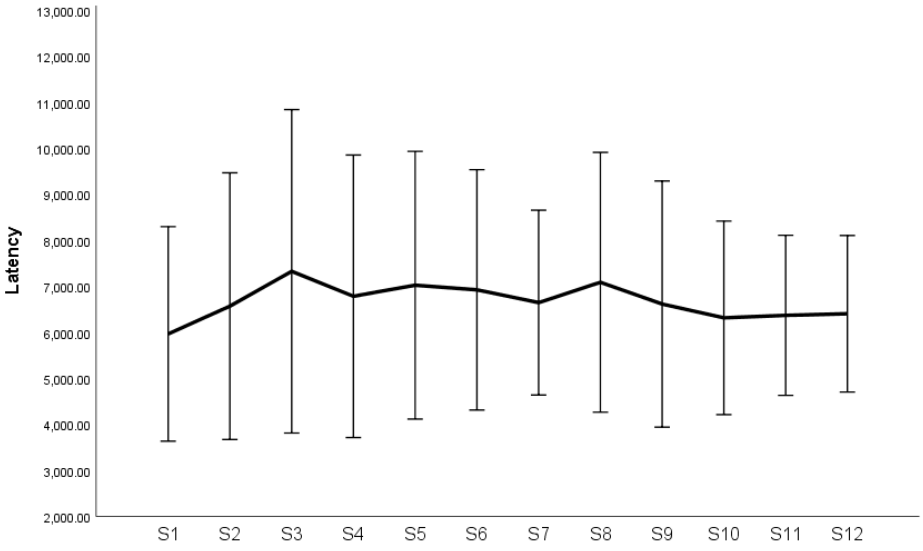


Figure 10. Spatial Span (SSP) – Median latency to last response

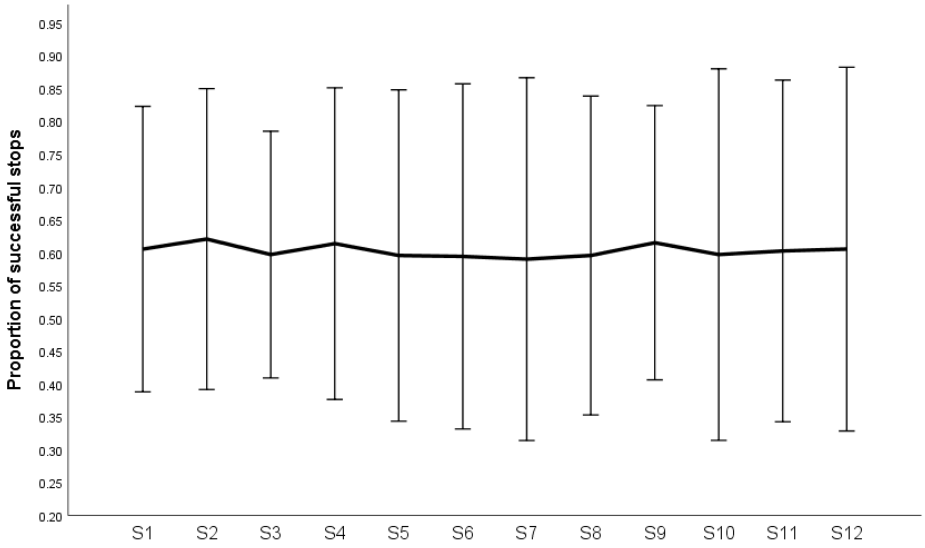


Figure 11. Stop Signal (SST) – Proportion of successful stops

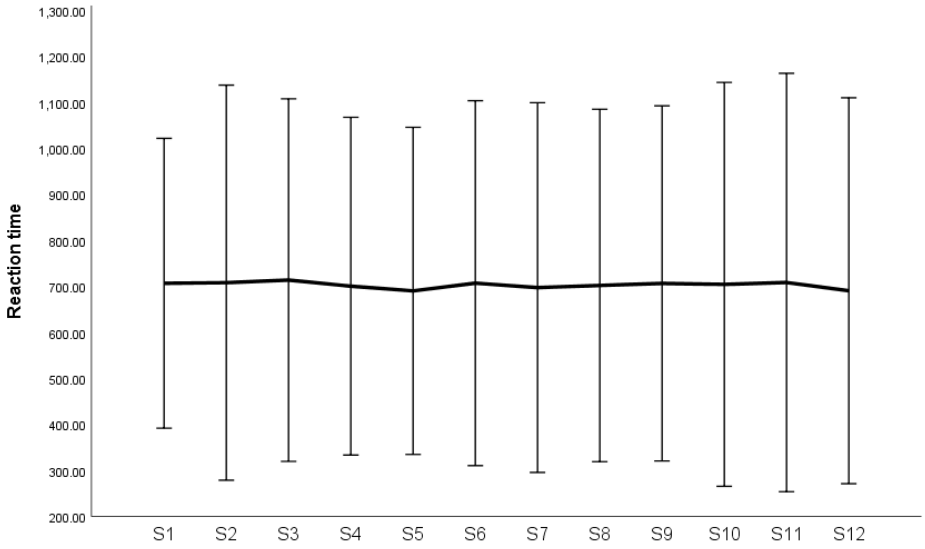


Figure 12. Stop Signal (SST) – Median correct reaction time

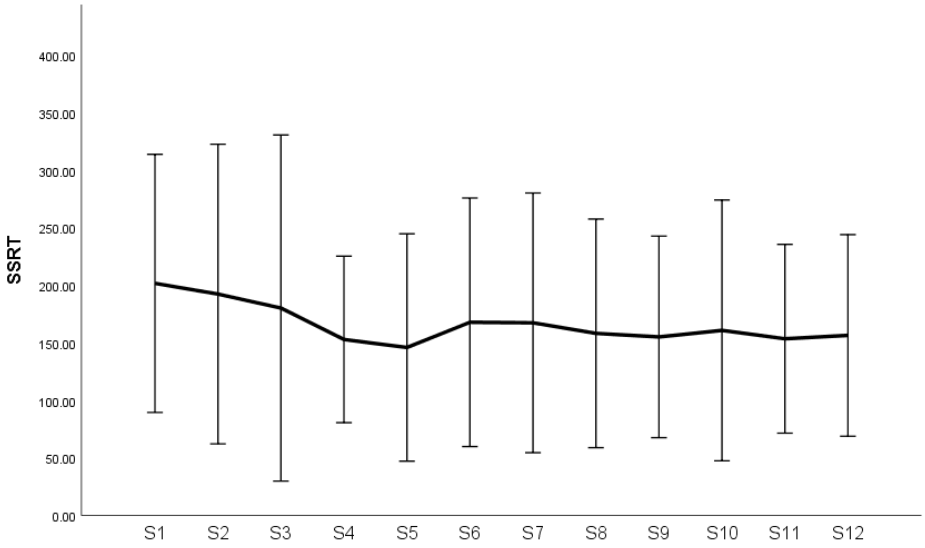


Figure 13. Stop Signal (SST) – SSRT

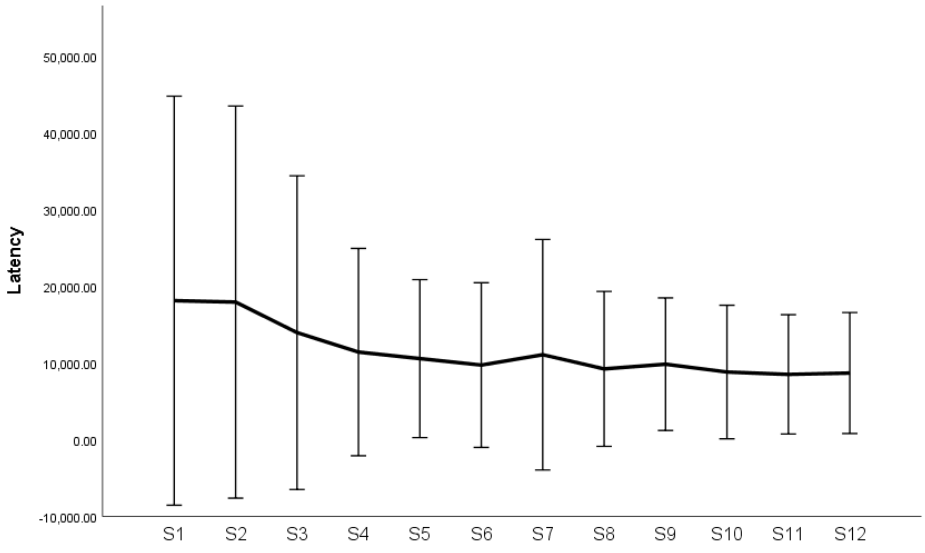


Figure 14. One Touch Stocking of Cambridge (OTS**)** – Median latency

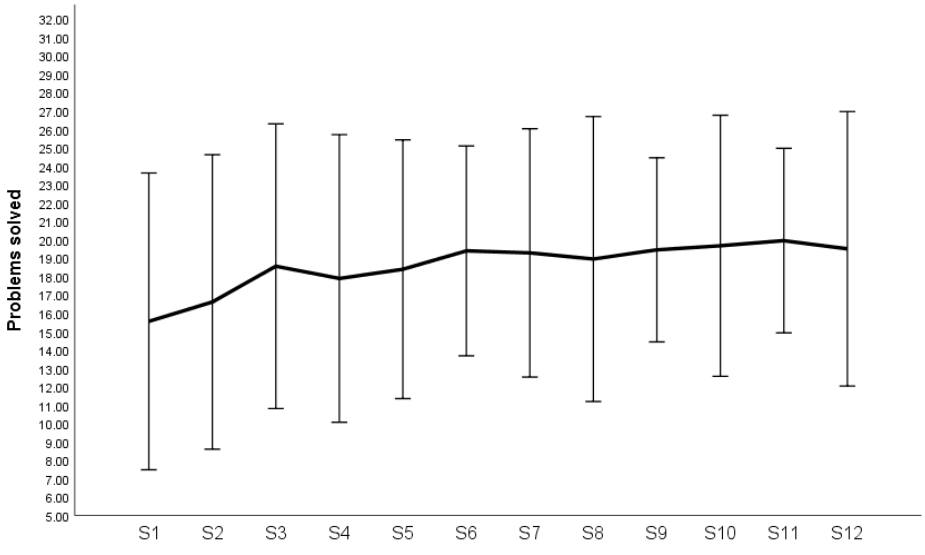


Figure 15. One Touch Stocking of Cambridge (OTS) – Problems solved on first go

Appendix X – COREQ 32 point checklist

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	
3. Occupation	What was their occupation at the time of the study?	
4. Gender	Was the researcher male or female?	
5. Experience and training	What experience or training did the researcher have?	
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	

Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	135
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	132
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	132
12. Sample size	How many participants were in the study?	132

13. Non-participation	How many people refused to participate or dropped out? Reasons?	132
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	132
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	132, 136
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	132-134
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	132
20. Field notes	Were field notes made during and/or after the interview or focus group?	133 (Appendix Y)
21. Duration	What was the duration of the inter views or focus group?	135
22. Data saturation	Was data saturation discussed?	
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	134, 135
25. Description of the coding tree	Did authors provide a description of the coding tree?	
26. Derivation of themes	Were themes identified in advance or derived from the data?	134,135
27. Software	What software, if applicable, was used to manage the data?	134
28. Participant checking	Did participants provide feedback on the findings?	
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	140
30. Data and findings consistent	Was there consistency between the data presented and the findings?	
31. Clarity of major themes	Were major themes clearly presented in the findings?	136-140
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	136-140

Appendix Y – Semi structured interview

The researcher: Okay so firstly I'm just going to give you a brief introduction to the rationale for the research.

The researcher: We know that individuals with type two diabetes are at an increased risk of brain decline compared to people without diabetes. Currently there is evidence lacking around interventions for preventing brain decline. We know that brain training has been shown to be an effective strategy for improving brain function in several different patient population groups. However, we do not know the effects of brain training in individuals have type two diabetes. We also know that brain training has been shown to increase the levels of a protein called brain derived neurotrophic factor that is associated with cognitive abilities, but again we don't know what effect brain training may have on that protein. So before conducting a large scale study. We first wanted to know whether it was feasible to conduct such a brain training intervention in individuals with type two diabetes. Therefore, the aim of the research was to investigate the feasibility of a six to eight week brain training intervention on brain function, and levels of BDNF in individuals with type two diabetes.

The researcher: So the primary purpose of this interview is to gain an understanding of the experiences and acceptability of those participants who took part in the cognitive training study. This interview will last approximately will last approximately 10 to 20 minutes, maybe a little bit over. Before we get started do you have any questions?

The participant: No

The researcher: And do consent to take part in this interview?

The participant: yes

The researcher: Great. So, we'll go first of all I'll just briefly remind you of what your involvement was. You obviously visited the university and completed a baseline assessment in which you were randomised to the train

training group. You then completed 6 weeks of brain training, completing 12 training sessions in total, followed by a post intervention assessment visit. So to start off with the brain training group, the brain training sessions. So first of all, how did you find the difficulty of the brain training task? Was it too difficult? About, right? Too easy?

The participant: It was probably about right because some of the tasks were more difficult than others and some of the tasks became easier the more that you did them, so I should think probably they were about right.

Commented [SC1]: Acceptability of training tasks, some that were challenging and some that became easier as the training progressed.

The participant: I know some of them were, they got easier because I think the difficulty didn't changes so much but some of them wasn't really a cap on the difficulty it was kind of a challenge every time I suppose

The participant: Some I found more difficult than others in any case just because I did.

Commented [SC2]: Shows the subjectivity of training tasks, some people will find some tasks more difficult than others.

The researcher: Yes of course and that's natural because everyone is different and everyone is going to find different things difficult but as long as you know, as long as you find you challenging I suppose that's the main thing. How did you find the length of the brain training session? Now, it was about 60 minutes. It may have been a little bit longer at the start because I was explaining the tasks, you were getting used to the tasks and so it is around 60 minutes

The participant: I think that's ok it wouldn't want to be any longer because I was conscious that afterward I was quite tired because obviously I was concentrating for that period of time. I guess I don't normally on to do that degree of concentration for that length of time for that intensity. So I think if you were to do it much longer I would expect your achievement to diminish just from tiredness rather than anything else

Commented [SC3]: Tasks we evidently taxing on individuals. 60 minutes is shown to be just about right for this person. Hints at loss of interest perhaps even boredom, but definitely a diminished performance.

Commented [SC4]: Think about the optimal amount of time per sessions, if 60 minutes is the upper most time participants preferred then perhaps shorter more frequent session may be more ideal

The researcher: Yeahh that's an interesting point because especially if people I suppose if they come from not doing brain training or anything sort of cognitively stimulating straight into something I can imagine at first it will be quite a shock to the system if you like but ok not that's great. That's a good point. So how did you find the amount of sessions performed each week. So it was twice a week

The participant: that was ok, no problems at all yeah

The researcher: Great. How about the overall length of the intervention so 6-8 weeks we tried to get the most people through, I think for yourself it was about 6 weeks. Was it?

The participant: It was ok, yeah. Because it was only 6 weeks, I mean ok I'm fortunate because obviously being retired meant that my time is easier to organise but for me that period of time to organise 2 sessions a week its fine

The researcher: It's not too bad. Great. And what about the study equipment so obviously I brought a laptop to your yourself. Was that fine?

The participant: that was fine. I used to use a computer every day and a tablet everyday

The researcher: Of course, a certain age a lot of people do have tablets and iPads, so I suppose it's nothing too new. So, did you find the brain training session enjoyable? Did you enjoy them?

The participant: yeah actually they were quite interesting. Annoying at times

The researcher: Of course I men its quite challenging it's what we set out to do. Yeah well its good to know that you find t enjoyable. Would you recommend this type of brain training so as in myself going to people's homes or coming to the university and doing this type of brain sessions? Would you recommend it to people?

The participant: yeah if they want to take part and that sort of thing yeah

The researcher: ok. Great so now let's get on to the brain training assessments so this is where you came in to the university at the start and at the end of the intervention and in terms of those tasks performed at the university how difficult did you find the tasks?

Commented [SC5]: Didn't seem overly affected by the frequency of sessions, could say it is definitely acceptable in this individual.

Commented [SC6]: Again retirement seems to be a big factor in whether this type of intervention is acceptable or not. Obviously no problems with this individual as not many other commitments to fit in.

Commented [SC7]: Technology in older population has become more and more acceptable. No problems using an interactive touch screen interface.

Commented [SC8]: Computerised cognitive training is acceptable to this person who did appear to enjoy it. However, again a common theme of annoyance and frustration with tasks is evident.

The participant: um moderate is suppose, I mean again, some were easier than others

The researcher: yeah I suppose (inaudible)

The participant: it is and some of them I think it's about probably about how your brain works and whether some particular sorts of task like patterns in numbers or whatever are easier for you or not so

The researcher: That's a very good point, I've had people that actually talk to me about how they prefer numbers to words and how it makes a difference I suppose, yeah you're completely right it will differ from person to person but um ok great. So how did you find the length of this assessment, so this is including taking blood The researcherples. So obviously taking blood The researcherples, the barn training battery it's about an hour, an hour 15

The participant: That's all right, that was fine

The researcher: do you think that this is suitable way for testing people's brain function? Using touch screen laptop, now I know there's all sorts of different ways you can do it, the most popular ones in the past were using pen and paper or pencil and paper. How do you feel about using a touch screen laptop?

The participant: I think that's fine, um I think I would find it more difficult now to use paper and pencil

The researcher: of course, yeah that's an interesting point yeah I suppose

The participant: I mean I write very little in terms of handwriting

The researcher: Yeah I suppose there's technology these days and all these laptops if you have got that sort of stuff you're more familiar with it.

The participant: That's it I would go to get information and all of that sort of thing. That's fine, I mean I suppose why wouldn't you.

Commented [SC9]: Similarly to the training tasks, assessment tasks varied

Commented [SC10]: Highlights the individuality/subjectivity around participants

Commented [SC11]: Acceptable extracting blood samples from this individuals

Commented [SC12]: Most suitable for this participant is using modern technology. I think this highlights that computerised brain training is the way forward. Pencil and paper si kind of a step back.

Commented [SC13]: Handwritten tasks may have had a detrimental impact on study participants

The researcher: yeah definitely yeah. Great um ok. So how did you find giving blood?

The participant: well it was ok, you did very well

Commented [SC14]: Blood extraction acceptable

The researcher: thank you very much its as I say to most people it does very in different people in some people its harder to do it

The participant: well I'm difficult to get blood out of so I've had people who had insisted on using my other arm because they can't use this arm and they don't believe you and eventually they come back again, well those sorts of things so yeah you did very well

Commented [SC15]: Perceived hesitation of participants with blood extract perhaps in some people because of the known difficulty they have giving blood.

The researcher: brilliant. And now I'll skip this one, the feedback because I actually haven't given you any feedback

The participant: no

The researcher: skip that part. Um ok we'll go on top the study locations not so did you find It difficult to travel to the university of Lincoln and the whole basically the visits from the university of Lincoln to parking to actually getting ot the building etc how did you find that?

The participant: It was ok I man the problem is always from anywhere in Lincolnshire it getting into Lincoln. Each time I came in as well we got two of us so we can find our way around obviously in terms of parking you arranged parking which is important because trying to park anywhere near here will just be a nightmare

Commented [SC16]: Obstacles traveling to the University, traffic into Lincoln is a big problem.

Commented [SC17]: Parking also a problem, probably why this participants preferred home visits e.g. traffic, parking etc

The researcher: Yeah it is

The participant: and then we tried to get into Lincoln by public transport form Grantham well we've only got the bus that takes forever, you can't get in by train unless you take trains so you're forced to driving so obviously it deepens on what the roads do, you know as well as I it will allow you to take 45 minutes or whatever it takes to get to Lincoln or it can take you an hour and a half

Commented [SC18]: Highlights the potential problems individuals face engaging in research in quite rural counties. This participant appears put off by such issues as parking, traffic, and public transport.

The researcher: Yeah I suppose relying on a train or a bus its annoying because they show up whenever they want to so yeah

The participant: So that's always going to be a problem

The researcher: Great. Ok, in terms of the study you were actually given the option of home visits or actually coming to the University of Lincoln to do the brain training sessions. I take it as you took the home visits you preferred the home visits

The participant: Yeah, I mean it's easier for me, it as simple as that really but particularly of you were going to do that number of home visits, sorry that number of sessions to then obviously be draining puts and extra time commitment. Pretty sure that you've got to fit the time in somewhere

Commented [SC19]: Although this individual was able to get to Lincoln, they chosen home visits purely for the convenience. I think this is a big factor with a lot of participants i.e. they would not have participated if home visits were not an option

The researcher: Yeah I'm in around for that study that's what I'm doing so to me that's, an actual commitment really, I can understand yeah. Ok so di you think an intervention like this would benefit more from like a group session?

The participant: how would a group session work? with people all doing the tasks or?

The researcher: yeah, I suppose its also we're thinking people coming to the university to do group sessions all at once

The participant: I think there's always going to be a problem if you wanted to look at the impact of something in an individual if you've got a group session you then add another dynamic to it, in a sense you find a group dynamic to it. I suppose its inevitable that people will say oh that's easy isn't it, no I find that really difficult

Commented [SC20]: Difficulties in group sessions potentially because of the subjectivity and group dynamics

The researcher: Yeah that's a good point

The participant: you know I think that sort if dynamic would have an effect you have to take into account whereas if you were doing it in an individual basis its

very much centred on how you respond to it. I think we talked at some point about the effect of physical exercise on people's health and even if you do that ok for some people that helps on a social basis, being a team and that because it gives the most motivation to do the exercise, but I think this is somewhat different

The researcher: Yeah it's quite individualised isn't it, it's quite personal in a sense I suppose so yeah ok that's great. What about a software lest say where you could log in and do the brain training yourself without someone coming to you? Would you think that's a good idea or something?

The participant: I think that's a possibility for again you mean those, it's those variables isn't it in a sense of where would you put that in place because you think that if you do that all the way through then that's perhaps not so easy because you have to learn how to do the task, there's the getting to the concentration element. I think that if you do it just by yourself on software on a machine your attention is diverted by something rather than giving 100% attention to the task

The researcher: yeah I suppose login in to the software has it benefits as you can do it in your own time along with you know its clear, you know what you're doing but it also has there downsides. People may find different things more difficult in their own etcetera. Ok we'll just move on now to talk about the study investigator. So did the researcher which is obviously myself make it clear the aim of the study? Did you understand that?

The participant: yeah

The researcher: brilliant. And was the task fpr each session explained clearly?

The participant: yeah it was each time. That was fine

The researcher: ok, and what about the study equipment did you find it easy using the?

The participant: yeah

Commented [SC21]: But on the other hand this participant seems to think that it could be beneficial in some ways e.g. socialising, being part of a team. But on the other hand there is that self-centred 'this should be about me only' approach

Commented [SC22]: Again this participant hits that I could be possible but there a lot of variables to consider e.g. subjectivity, commitments etc Some people work well alone where as some need that motivation from face to face sessions.

The researcher: and least of all did you find the researcher approachable?

The participant: yeah

The researcher: ok brilliant so thank you for taking part